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ORIGINAL ARTICLES

ON THE SUBJECT OF ORDERLY OR LAWFUL BEHAVIOR

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MANY physicians who have been interested in attempts to modify the rules of child management so that it may conform more closely to the normal growth and development of children have been criticized for allowing them "to do anything they want." It is said that "self-expression" is advocated to the point of license in attempts to take the pressure off of the youngsters; that obedience and discipline are forgotten; in short, that a sort of childhood anarchy is being fostered.

These statements are made in spite of the fact that it is obvious that most physicians involved in studying the mental hygiene of childhood are vitally interested in good, rather than bad, behavior. Many such men, often fathers and grandfathers themselves, are considerably irked at the implication that their efforts are considered to be socially disintegrating. It is evident that a basic misunderstanding lies back of such a situation.

Any person at all familiar with the development of children in modern times must be impressed with the fact that no one can grow up and live a happy life today unless he learns to conform to the major tenets of social custom. This means that no doctor with any sensitivity to children's needs will advise that they be allowed always "to do as they please." Everything that is said in this article is designed not to promote license, but to make conformity possible where it has been extremely difficult or impossible to achieve in the past.

This paper, therefore, discusses first, the social situation that exists today as a setting for bringing up children; second, the laws for behavior as we find them at present; third, the methods available for controlling behavior; and, fourth, what changes can be made in our codes to obtain more orderly and lawful behavior in young children.

I. THE PRESENT-DAY SITUATION

Whether one looks at modern environment from the viewpoint of the world, nation, municipality or family as a place in which to rear children, the impression one gets is that of intense disorganization.

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The *world,* having emerged from two devastating wars, is finding great difficulty in establishing any consistent formula for permanent international law or peace, even under the threat of atomic weapons. Our own *country* is plagued by internal economic, racial and social problems which seem insoluble and which are not even being attacked in a forthright scientific manner. Instead the issues are being confused by emotionalism and name calling. *Cities* and *towns,* in addition to facing these same national problems, have to contend on the one hand with juvenile delinquency and on the other with a threatened breakdown in their systems of public education due to lack of tax support. On the *family* level, parents find themselves confused by the lack of sincere civic leadership, distressed over the difficulties of child management and, because of their perplexity, reacting with a great variety of methods of child care in a more or less haphazard fashion. As a place in which to rear children who are to grow up mentally, emotionally and physically sound, one could hardly select a more difficult environment than the one that exists in this present era.

However, it is somewhat encouraging to find that in the field in which we are most interested, that of pediatrics, some steps are being taken toward settling many of the problems at each of these levels.

Nutritional relief for children is going on, under the United Nations organization, backed up by *all* nations, in front of and behind the iron curtain. On the national level, the American Academy of Pediatrics in its present survey of facilities for children's care is making an unprecedented attempt to bring order out of chaos at this specific area of national concern. In many municipalities we find pediatricians who are interested not only in the physical care of their patients, but also in their mental and emotional progress and in their educational opportunities. They often express this interest in the conduct of their private practices and in their promotion of child guidance centers, juvenile courts and similar agencies.

All of these pediatric activities would be grounds for considerable satisfaction were it not for the fact that in comparison with the clamor of the world they amount to little more than "the still, small voice" in the wilderness.

In order to strengthen their efforts to bring order out of chaos in child behavior, physicians need to promote a clear, unified program of education on a broad family level. In order to carry this out we must first decide on scientifically sound procedures and then put them into general practice, at least as far as medical control is concerned. This would imply devising a set of rules and principles governing child behavior which every physician could support. It would, if carried out, relieve the confusion which exists in families and give our children a chance at least to know what is expected of them. Perhaps they could, if we were wise enough in our selection of the regulations, begin to shape their lives in a more orderly and lawful manner.

II. The Laws Governing Child Behavior

To understand this subject we must realize to begin with that every child in the world today finds himself in the dilemma of trying to exist under two sets of laws which often conflict in their most intimate and important details. I refer to the laws of civilized living and to those inherent ones based on human growth and developmental urges (Table I). It will help if we consider these two sets of regulations as to their origin, uniformity and acceptability.

(a) The laws of civilized living are, by comparison, very recent, almost newborn

in origin. They have been devised, for the most part, to adjust individual behavior to the exigencies of community living and, therefore, differ widely in various localities, even in different parts of the same country, state or town, according to the various economic or cultural groups involved. They may and frequently do shift with minor influences such as even the change of medical advisor or the arrival of a new pastor in the church. The social laws are imposed from without, a characteristic that makes them difficult to live up to by anyone, large or small.

In fact, when we look upon our man-made set of regulations governing child care we cannot but be impressed by their recent origin, their changeable nature and by a variability in types so great as to make them seem like shifting sands. Yet we expect

TABLE I

TWO SETS OF LAWS UNDER WHICH CHILD TRIES TO EXIST

Laws of social order	Laws of growth and development
Of recent origin	Ancient
Adjust individual to society	Protect individual in life struggle
Differ in localities	Uniform in all localities
Differ with culture	Uniform in all cultures
Differ with economic state	Uniform in all economic groups
Complexity due to variability of laws	Complexity due to control of many parts of the whole body but effect is unifying
Acts upon organism from without	Acts upon organism from within
Often not easily acceptable	Usually highly acceptable

each and every child to be able to make the necessary adjustments to conform to their demands.

(b) The laws governing human growth and development contrast markedly in all these respects. They are more ancient than the race, stemming back uninterruptedly to the origin of life. They were quite evidently devised to protect the individual in his struggle for existence in an adverse world, and are so fundamental that it would be utterly impossible to survive at all without their insistent drive. They are, for the most part, quite uniform in their major aspects although individuals do differ in details. (For instance, while every baby has a feeding rhythm, not all are set at the same interval.) There are no variations in growth laws due to economic or cultural influences. The laws of growth work from within as an integral part of the individual and belong to him; therefore, they are easily obeyed.

Summarizing these regulatory systems, we find that one is recent, aimed at adjustment to civilized living, extremely variable and imposed from without, while the other is ancient, protective, uniform and inherent.

In the light of the differences just outlined in the two codes for living which influence each child born into the world it should be evident that when the two systems oppose

each other, confusion and inefficient or unapproved behavior will be inevitable and that orderly and lawful behavior will be more easy to obtain if the two codes synchronize by chance or purpose. It should be remembered that, since growth laws are unchangeable, any adjustment of such tendencies must be made voluntarily and habitually by the child so that he overrules or controls his inherent urges, a quite mature accomplishment. The problem then resolves itself into (1) how to influence the child to control his growth urges enough to conform to social laws or (2) how to modify social laws to conform to the nature of growth.

III. Methods for Controlling Behavior

The first method of solving the problem, of course, introduces questions of what technics of training and discipline we can use to obtain these necessary adjustments. The methods most commonly used may be divided into those which rely chiefly on the powers of persuasion including guidance, example and verbalized instruction and those which rely mainly on corporal punishment or force. It is obvious that the employment of some such method is imperative, especially where natural urges, if carried out, would be dangerous. Children have to be taught to avoid such situations even though their developmental tendencies are insistent. I am speaking of the dangers of stoves, electric light sockets, traffic, water and so forth.

The nonpunitive methods are highly effective if the child remains in a friendly emotional relation to his teachers, and are by all odds the most useful technics we have at our disposal. As used in our society, however, they are open to certain criticisms. They can be overdone in a censorious way so that the child feels unnecessarily guilty. In a quantitative way they can be overdone so that he is nagged most of his waking hours. Both of these mistakes may lead to unfortunate results. In the first instance an inferiority feeling based on guilt may result, and, in the second case, an unnecessary frustration tinged with antagonism toward those who care for him may be engendered.

Although frictionless conformity to social laws is impossible in our culture, a great deal can be accomplished by intelligent use of persuasive measures, especially if they are backed up by good example. More effective use of persuasive measures should be a matter for study by all those interested in child behavior.

The other method, in which emphasis is placed on *physical punishment,* has also been used freely in our training and disciplinary programs. It has obvious advantages and disadvantages which must be considered before its value can be appraised.

In favor of corporal punishment, spanking for the most part, is the fact that it is spectacular and is likely to be remembered by the recipient as a definitely unpleasant result of his unapproved behavior. Furthermore, it gives the donor an opportunity to release any angry emotions aroused by the child's acts. As a result, the child may emerge from the episode having learned the unfavorable consequences of his dereliction and the adult may emerge with the satisfying emotional feeling of having defended his sense of proprieties and having become free of any resentment that might have persisted had he withheld his hand. In favorable cases a lesson is learned without too much harmful reaction. In order for this to happen, however, the parent must be able to make it clear to his child that it is the unapproved *act,* not the child, which is bad.

On the other hand, corporal punishment is open to some very obvious objections and has some dangers.

By and large over the years, it has failed to get results. One need only to point out that in spite of the fact that it has been almost universally applied, our guidance clinics, juvenile courts, penal and mental institutions are crowded with large numbers of our population who have not learned to conform. And furthermore, those in charge of such institutions almost unanimously state that the majority of their patients suffer from having been subjected to over-rigid discipline in childhood. This over-all failure is the strongest argument against corporal punishment.

In the second place, it heightens adverse or resentful responses in the child so that after punishment he actually may be less, rather than more, inclined to conform. Since the ultimate aim of all disciplinary efforts is to produce people who will comfortably conform to the rules of society, this is a serious defect in the method. In addition, it is evident that where conformity is obtained it may result from fear of, rather than from affection for, the parent, a dangerous mental attitude to establish in any child.

And finally, it should be stated that the idea that corporal punishment is an inherent right in which every parent may freely indulge is an actually dangerous concept. During three years at a large city hospital we observed three children, one an infant, one two years old and one of about four years, who were actually killed by corporal punishment. Two had skull fractures and one a ruptured liver. At the coroner's inquest in all three instances there was the attitude that it was too bad, but the child was dead. What could be done about it?

During the same interval many minor injuries were treated, ranging from fractures to burns inflicted by parents. These instances seldom are reported in our lay or scientific papers. But if there were any way of discovering the number and character of injuries to children resulting from corporal punishment it is certain that the figures would cast a very unfavorable light on its value as a freely approved procedure.

It is only fair to state then that, while corporal punishment is and has been an almost universal method for obtaining conformity, it is only partially successful and is often open to the objections that it is a questionable method from the standpoint of adverse emotional reactions and even may be dangerous to life and limb.

IV. Modification of Codes to Make Lawful Behavior Possible

This brings us to a consideration of the second possible method of adjustment; namely, the modification of our civilized codes to fit more closely those of growth. This proposal may sound radical or weak-kneed to those whose ideas of right and wrong are rigidly set in their own particular patterns of behavior, be they cultural, social or medical. But they will sound decidely conservative to those who are adaptable enough to see the complexity of the children's problem and who are practical enough to utilize a method which has some chance of success in a field which up to now has been notoriously unsuccessful.

We are speaking here of modifying our codes for the care of young children during a period when the changes will have little adverse effect on the general social structure and when habits of obedience and self-discipline are formed. Specifically, I am thinking of the regulations governing our care of newly born babies, particularly of our response to their individual needs for care and feeding. I am referring to our methods of training in eating, sleeping and eliminative functions in infancy. I am including our technics of obtaining obedience and self-discipline during the second and third years of life.

And I want to consider also our methods of teaching children how to adjust to other people in the pre-school and school periods.

Time permits mention of only a few of the antipathies between social and growth codes. It will then be up to the individual to decide which social regulations may be modified in the interest of simplifying the child's problem.

Shall we decide that the screaming newborn should always be left to cry it out, or shall we fondle him, change him or feed him, whichever seems appropriate, whenever he cries?

Shall we modify the prescription of rigid feeding intervals and amounts of formulas so that young babies can be fed when they are hungry and as much as their growth urge demands?

Shall we require babies of a few weeks or months to conform to our time and place of bowel evacuations or shall we delay training until they are old enough to know what it is all about?

Shall we allow a baby's tired feelings to indicate when and how long he naps or sleeps at night, or shall we try to regulate him by the clock?

Shall we "break" babies of the two A.M. feeding at birth or shall we allow them to be fed when they wake up at night and omit this feeding when they show an inclination to sleep through the night?

Shall we "break" them of the bottle at a specified age, or allow them to throw it away when they decide it is no longer wanted?

Shall we try to "break" them of thumbsucking, or shall we allow this sucking urge to be satisfied in this manner until it too gradually fades out?

Shall we insist that the young toddler refrain from touching all of our adult gadgets when the urge for exploration and manipulation obsesses him, or shall we give this urge a chance to express itself and teach him selectivity with one restriction at a time?

Shall we attempt to make the two year old generous with his belongings, or shall we bow to his nature and wait until his growth makes possible the expression of sharing with others?

Shall we train all children to use the right hand, or shall we be willing to recognize his individual differences as such?

Shall we, in the preschool years, insist on strict truthfulness, or shall we tolerate the natural tendency of phantasy falsehood which is so characteristic at this age?

In the school years shall we insist on a rigid schedule in the subjects to be taught, or shall we recognize that many of them are learned best after maturation points in each child's mental growth have been reached and adjust the curriculum accordingly?

Obviously, page after page of such questions could be listed, each one posing the same problem: to what extent are we willing to adjust our social, medical or educational laws for child behavior to the realities of human nature? Taken individually, these conflicts may appear trivial, but when one realizes that in many instances most or all of these conflicting regulations are rigidly adhered to, it is not hard to understand why children are confused and why their behavior reflects this attitude. One would expect to find them either erratic and antagonistic or completely cowed and subdued (thoroughly "broken"). The first result is certainly not orderly and lawful and the second we know by experience is the one which often leads to a mental institution in later years.

On the other hand, if we are willing to relax in our insistence on rigid conformity to

the usual man-made regulations and can make up our minds to expect children to act their growth age, much of the conflict in the two systems governing behavior can be removed. This can and does eliminate much of the confusion and frustration of young children and leads to more orderly behavior and, what is more important still, it tends to allow children to emerge from their early years with a positive attitude toward conformity rather than with one of pugnacious negativism or complete withdrawal.

The application of such technics in child management requires one attribute in adults which is hard to come by, extreme patience—the willingness to wait for growth to make possible the kind of perfection we ultimately expect. Understanding is essential, but it is not enough unless complemented by a sort of kindly patience tinged with confidence in the possibilities of human development.

Summary

The problem of orderly and lawful behavior in young children has been faced realistically. It has been pointed out that infants and young children are influenced by two sets of codes: one, those prescribed by civilized man, and the other by their own inherent growth impulses. The characteristics of the two codes were mentioned, pointing out that the former were of recent origin, extremely variable in different geographic, cultural and even medical situations, and were imposed from without; and that the latter were of extreme antiquity, were on the whole consistent in every social set-up, and exerted their force from within the individual.

It was shown that when the two systems regulating child behavior conflict, it is necessary either to train the child to ignore his growth urges in an effort to conform to social dictates or to modify these requirements. The growth demands cannot be changed. The methods by which a child can be made to conform are by persuasion, including example and guidance, or by corporal punishment, neither of which is a perfect method.

Illustrations of many aspects of behavior in the young child in which conflict commonly is found were cited to give some idea of in how many respects young children may be confused or frustrated with resulting unapproved behavior. It was emphasized that much of this might be prevented by relatively unimportant changes in the man-made codes.

It should be emphasized again that the whole purpose of this discussion is to make conformity to our laws possible and to insist that no child today can grow up doing entirely as he pleases. The adjustments called for are often merely those of timing, of demanding conformity at a later, more reasonable developmental stage.

Conclusion

Since children are influenced by two codes of behavior which often conflict, the pediatrician has an opportunity to exert his influence toward removing these conflicts in the interest of lawful child behavior.

The Golden Rule has persisted through most civilizations and religions ever since man has recorded his acts. If he had even approximated obedience to this great law, this article would not have been necessary.

SPANISH ABSTRACT

Sobre La Conducta Propia y Juiciosa

Muchos medicos interesados en modificar las reglas del manejo de los niños para conformar o dirigir su desarrollo normal estan conturbados por el hecho de que sus esfuerzos son incomprendidos y piensan que a ello contribuye el descuido en la obediencia y disciplina.

Este trabajo considera primero, la situacion social que existe hoy como un fundamento para el progreso del niño; segundo, las reglas de conducta tal como las encontramos hoy en dia; tercero, los metodos aconsejables para el control de la conducta y cuarto, los cambios que pueden ser introducidos en nuestros codigos para obtener una conducta mas propia en nuestros niños pequeños.

Se señalan los siguientes puntos: 1. El ambiente hoy, esta intensamente desorganizado y poco adaptado a los buenos cuidados del niño. 2. Todo niño esta influenciado por dos tipos de codigo de conducta: El primero lo establece su propio ambiente civilizado, es reciente en origen y tiene como objetivo el ajuste a la vida de la civilizacion. Es extremadamente variable y es impuesto de fuera a adentro. El segundo, esta ordenado por sus proprias fuerzas de desarrollo, es antiguo, proteccionista, uniforme e inherente asi mismo.

Como quiera que estos dos codigos a menudo se oponen el uno al otro, el niño esta en dificultad para comenzar de donde la confusion y la conducta impropia son el resultado. El problema radica en determinar como influenciar en el niño para controlar su desarrollo de una manera suficientemente conformada, o como modificar las leyes sociales para adaptarlas a la naturleza del crecimiento del niño.

Los metodos para obtener la mejor conformacion son aquellos en los que se emplea la persuasion, sin castigo, frente a aquellos que emplean el castigo corporal. Ninguno de los sistemas empleados hoy, son perfectos.

Se concluye que en cuanto a la edad temprana de la niñez se contrae, un comportamiento normal es mucho mas facil de asegurar si los codigos pueden ser ajustados a los hechos reales del crecimiento. Estos ajustes incluyen practicas materias relacionadas con el recien nacido, la adopcion del sistema de autoregulacion del alimento, el entrenamiento en el uso del toilette cuando ya el niño es suficiente para cooperar, ajuste del habito del sueño, en sintesis el reconocimiento en nuestras reglas de conducta de la definitiva maduracion en cuanto al desarrollo del niño, cuyas necesidades deben ser respetadas.

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LIPOID NEPHROSIS

Clinical and Biochemical Studies of 40 Children, with 10 Necropsies

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OUR purpose is to present experiences gained from the study of children with nephrosis observed in the Children's Hospital of the State University of Iowa during the past 15 years. The diagnosis of nephrosis was made only when the following criteria were met: presence of edema, proteinuria, good renal concentration ability, high blood fats and low blood protein with marked decrease in the albumin fraction; absence of retinopathy, persistent azotemia, persistent hypertension, and hematuria other than an occasional finding of about 10 RBC for each high power microscopic field in a centrifuged, freshly voided specimen. Only one child is included who did not meet all these criteria. Children who eventually showed evidence of chronic nephritis have been excluded. However, the clinical course of two such children is discussed.

With few exceptions, all the children were examined at regular intervals throughout the study. Information was available in 1947 for all but one. Children observed for less than one year have been excluded except when death occurred while under observation. The group consisted of 26 boys and 14 girls. Of the 40 children 14 were 6 years of age or older at the onset of illness. The youngest was 15 months, the oldest 15 years.

The total duration of the disease was less than 6 months for 17 children, between 10 and 30 months for 13 children and more than 4 years for 15 children. The shortest course was seen in a boy 3 9/12 years old, who died 2½ weeks after onset. The longest course was observed in a girl 15 months old at onset, who had evidence of active disease for 7 years; she has been well for the past 6 years and is now in good health at 14 years.

Of the 40 children, 26 are alive, 19 have been entirely well for from 1 to 16 years, 3 have been well for less than a year, 1 has proteinuria without edema and 3 have active disease.

From a review of published mortality rates, it is apparent that the children should be divided into two groups; those who died before and those who died after the advent of sulfonamides. Aldrich[19] states, "Before chemotherapy, 88% of the patients with nephrosis, who developed bacteremia and peritonitis or other severe infections, died of the infection. After chemotherapy, the mortality from severe infections dropped to about 40%." The same author reports a mortality rate of 30% in a recent survey of patients with nephrosis. Davison and Salinger[23] in 1927 reported 6 deaths among 19 children whose illness lasted at least one year, or a mortality rate of 32%. Schwarz, Kohn and Weiner in 1935 reported a mortality rate of 55%. Farr in discussing the report of Schwarz, Kohn and Weiner stated that the mortality in a group of 36 patients observed for six years was 44%. Of 22 children in our series who had the disease after sulfonamides

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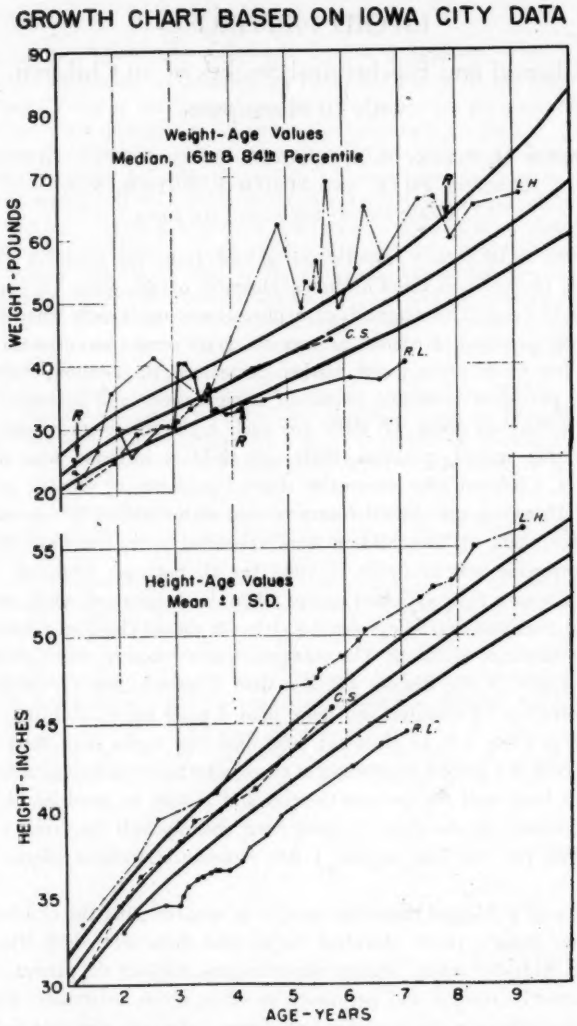

CHART I. The growth of three boys during the course of active nephrosis and after recovery.

became available, only three died, including one with Esch. coli bacteremia which does not yield easily to sulfonamides. Excluding three children who still have the disease, the mortality rate for this group is 15.8%. It is reasonable to assume that nephrosis in children observed after sulfonamides, penicillin and streptomycin became available will have an even lower mortality rate.

The nutritional history prior to onset seemed to have no relationship to occurrence of nephrosis; it was satisfactory in the majority. Breast feeding did not seem to offer any advantage; of 36 children of whom the type of feeding during infancy was known, twenty-three were breast fed for more than three months and four for less than three months.

TABLE I. Analysis of 26 Living Patients

No. and Sex	Age Onset, Yrs.	Essential Findings (a)	Hematuria (b)	Special Features During Illness (c)	Treatment (d)	Duration (mos.) (e)	Present Condition (f)
1. M.	4½	L+	0	Steady improvement	Choline, Liver extract. *S.*	10	Well over 3 yr.
2. M.	6	T+ L+	3–8 on few occas.	Severe cerebr. edema; hydrothorax*	Sucrose; bile salts; urea; amm. cl. *S* & *P* conc. alb.	—	Active disease
3. M.	1½	Nothing remarkable	0	No recurrences after edema subsided	Amm. cl. Vit. B complex *S.*	5	Well over 2½ yr.†
4. M.	2½	Pneumonitis	0	Otitis media, followed by improvement	Choline; Liver extract; *S.*	3	Last exam'd. 1944 Was well then. Not heard of since.
5. M.	6	T+ sinusitis	0	Many f. of e.; pulmonary edema	Amm. cl.; sucrose; fever-Rx; T & A	8	Well over 8 yr.
6. M.	1½	Pneumonitis L+ sinusitis	0	Otitis media, several times; many f. of e.	Thyroid T & A	8	Well over 16 yr.
7. M.	1½	T+ pleural effusion sinusitis	4–5 on one occas.	Fever for long time	Thyroid; amm. cl. T & A	5	Well over 11 yr.†
8. F.	2½	L+	0	Chickenpox in recovery phase.*	*S.* & *P.*	3	Well over 2 yr.†
9. M.	1½	Urticaria; L+; sinusitis chron. bronchitis	4–5 on two occas.	Many f. of e. and crises*	Choline; mercupurin; sucrose; amm. cl.; *T.* & *A.* *S.* & *P.*	78	Well over 1½ yr.†
10. F.	9	Swell. nasal turbinates; sinusitis	0	Fast recovery	Blood and plasma; *S.*	1½	Well over 5 yr.†
11. F.	2½	Nothing remarkable	0	Chickenpox, during recovery phase	Choline *S.*	2½	Well over 3½ yr.†
12. M.	1½	Conjunctivitis	occas., many times	Bronchopneumonia; severe anorexia	Vit. E; *S.* & *P.*	15	Well over 1½ yr.†
13. M.	2	L+	occas., various times	Otitis media; rubella; many f. of e.	Choline; thyroid; *S.*	27	Well over 3 yr.†
14. M.	6½	Dullness of lung-bases; pleural effusion.	0	Fast recovery; some recurrences	*S.*	17	Edema ceased 1 yr. ago; albuminuria ceased 3 mo. ago†
15. M.	7½	Otitis; sinusitis	0	Once anuria*	Mercupurin; *S.*	—	Well over 2 yr.
16. F.	6½	L+ Sinusitis	0	Developed hydrothorax	Choline; *S.*	60	No edema for 2½ yr. but still has albuminuria†
17. M.	11½	Nothing remarkable	0	Septicemia*	*S.* & *P.*	2	Well over 3 yr.
18. M.	2½	Asthma L+	0	Several crises, one foll'd. by improvement, many f. of e.	*S.* & *P.* Sucrose Urea	—	Disease active
19. F.	4	Nothing remarkable	2, once	Had rubella, followed by temporary improvement	*S.* & *P.*	6	Well 4 mo.†
20. M.	1½	Otitis	0	Rapid improvement*	*S.*	1	Well 3½ yr.†
21. F.	1½	L+; purulent rhinitis	0	Appendectomy. Many f. of e.*	Acacia. Mercupurin	84	Well 6 yr.†
22. M.	3½	L+; sinusitis	Pronounced, often	Many f. of e. Myringotomy; antrotomy*	Sucrose; Thyroid	54	Well 7 yr.
23. M.	2½	Rt. sciatic paralysis, post salyrgan inject.	0	Nothing remarkable	$MgSO_4$	12	Well 6 yr.
24. F.	1½	L+	occas. once many	Few crises. Many f. of e.	Choline; *S.* & *P.*	—	Active disease
25. F.	3	Sinusitis; eczema	0	Lost edema in 1 mo.	Thyroid; Salyrgan	4	Well 9 yr.
26. M.	16	L and spleen+; chronic osteo.	0	Developed diabetes*	Choline; *S.*	—	Well†

Key: (a) L—Liver; T—Tonsils—+—Enlarged. Edema with or without ascites is not recorded, as it was present in all cases.
(b) Red blood cells, per high power field, centrifuged specimen.
(c) f. of e.—fluctuations of edema.
(d) Blood and/or plasma transfusions not recorded; most patients received one or the other or both; S—Sulfonamide; P.—Penicillin
(e) From onset of symptoms to complete recovery without recurrences or albuminuria.
(f) "Well" means absence of symptoms, edema and albuminuria.
* Patients discussed in text. † Means child was examined in 1947 and blood values were normal.

Because of the role that immune bodies may play in nephrosis, we reviewed the incidence, prior to onset, of commonly given immunizations and of the usual childhood diseases. By far the majority of the children had received one or more immunizations or had had one or more of the common communicable diseases, or both, before they became ill with nephrosis.

Upper respiratory infections preceded the illness as often as not. Regardless of the relationship at onset, these infections were responsible for a high proportion of recurrences in children in whom the disease had been inactive for various periods of time.

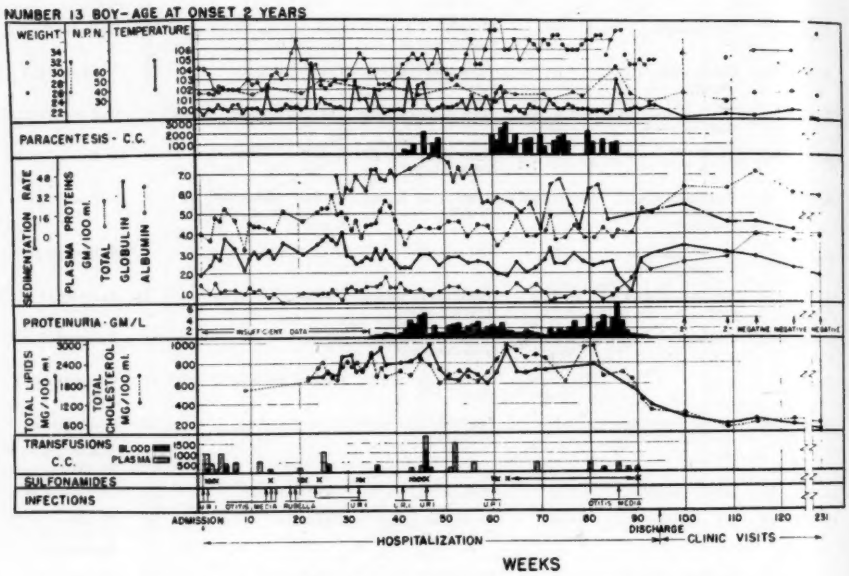

CHART II. The course of nephrosis for R.L. (Case 13) during his hospitalization and care in the outpatient clinic.

Sinusitis was found with considerable frequency, but we could not duplicate the observations of Clausen[1] in 1924 who found sinusitis in all of 11 children with nephrosis. He postulated that staphylococcal infection is the cause of nephrosis. The nephrotic children of our group who had maxillary antrum washings did not show dramatic improvement even when purulent material was evacuated. However, various staphylococcal infections were present frequently. We have observed otitis media, sinusitis, osteomyelitis and septicemia, each caused by hemolytic Staph. aureus.

Enlargement of the liver at some time during the course of the illness was found frequently. Invariably the liver size decreased during recovery.

Nine children had allergic manifestations, such as asthma, urticaria, food allergies or unexplained eosinophilia. Eczema was conspicuously absent. The presence of allergy may well have been coincidental, but we considered it noteworthy.

We like to stress the importance of early recognition of the disease, because therapy has been found to be most effective in the early stage. However, the duration of the

illness and the number of recurrences did not seem to impair the prognosis for either life or eventual complete recovery. Those who recovered had no apparent residual damage. Growth and development were uniformly good, even of children with many and severe exacerbations (Chart I).

Table I presents a summary of observations on the 26 children of this series who are living. The majority followed the typical course of nephrosis, often and amply described in the literature. Leiter,[2] among others, has published an exhaustive review of the disease. Chart II portrays graphically an example of the course of the illness in terms of temperature,

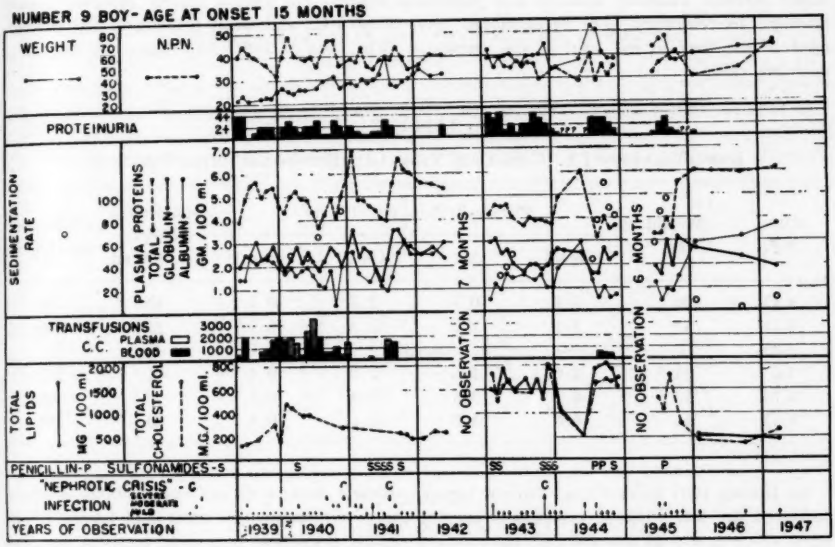

CHART III. The course of nephrosis for L.H. (Case 9) over a period of eight years when he was hospitalized on various occasions and regularly visited the outpatient clinic.

weight, nonprotein nitrogen, blood proteins, lipids, proteinuria, hematuria, sedimentation rate and therapy. The following discussion is of children who presented features of special interest.

CASE REPORTS

Case 2. H.A. This child was one of two who developed cerebral edema during the course of the illness. He had also bilateral hydrothorax, was dyspneic, cyanotic and critically ill. Immediate lumbar puncture appeared life-saving. In addition, 1,500 ml. and 2,400 ml. of fluid were removed from the pleural and peritoneal cavities respectively, and magnesium sulfate was injected intramuscularly. The child had shown marked shifting of body fluid on various occasions, and it is at such times that cerebral edema is prone to occur.

Case 8. J.E. This child demonstrated the great care required to evaluate reports of cures. Although it was not a remedy but a disease that seemed to carry this child to recovery, it must be remembered that many forms of therapy may appear to be effective if administered at a time when the child is in a phase of spontaneous recovery. This girl contracted varicella. At first it appeared as if recovery occurred as a result of varicella. Study of Table II, however, demonstrates that prior to varicella she began to lose edema and that the serum albumin values were increasing. Recovery was permanent and there was no recurrence.

Case 9. L.H. This boy is of special interest because he had active nephrosis for 6½ years, but apparently has made complete recovery. He received very large amounts of plasma transfusions with little effect on the disease. The number of severe infections he survived is noteworthy. He entered the hospital May 1939 at the age of 15 months. Two weeks preceding admission he became ill with fussiness, edema of the eyelids, urticaria and proteinuria. He was fretful, poorly nourished and markedly edematous. Results of laboratory studies are recorded in Chart III. After leaving the hospital he was taken to Arizona where he seemed to get along nicely. On the way back to Iowa edema recurred and the father gave him an intragluteal injection of a 50% solution of magnesium sulfate, which later resulted in abscess formation. Readmitted to the hospital, he was found to be severely edematous. He had a thick nasal discharge and rales in the lungs. Roentgenograms revealed bilateral maxillary sinusitis and pulmonary fibrosis. The gluteal abscess required surgical drainage. In November 1940 he developed fever of 40.8°C., abdominal tenderness, and enlargement of the liver to the level of the umbilicus. WBC was 36,260/cmm. Apparently he had a nephrotic crisis.

TABLE II

BLOOD VALUES OF J.E. (CASE 8), 2¾ YEARS OLD, BEFORE AND AFTER VARICELLA

Date *1945*	Weight kg.	Plasma Protein, gm./100 ml.				Non-protein Nitrogen mg./100 ml.	Cholesterol mg./100 ml.
		Total	Alb.	Glob.	Fibr.		
2-13	20	3.8	0.7	2.5	0.4	40	422
2-21	15	5.1	1.2	3.3	0.6	22	443
2-25	—	—	Varicella		—	—	—
3-6	14.5	4.6	1.6	2.6	0.4	41	550
4-10	13.5	6.1	3.3	2.6	0.2	—	366
8-22	15	6.6	4.2	2.1	0.3	40	258

In January 1941 he developed atypical papular urticaria. Remissions and exacerbations of edema continued. In July 1941 he experienced another crisis, accompanied by erysipeloid lesions of the thigh which developed into abscesses and required surgical evacuation. Because of persistent purulent nasal discharge, antrum washings were performed in June 1942. In December 1942, at the age of five years, edema again was severe. There still was mucopurulent nasal discharge. He also had pharyngitis and rales in the lungs. In October 1943 he developed severe anasarca and generalized as well as pulmonary edema. Under treatment with sulfathiazole he improved. After discharge from the hospital he was given prophylactic doses of sulfathiazole. In June 1945 he returned for examination, stating he had not been free from edema at any time. However, since January 1946 he appeared to have recovered. Since then he has been free from edema and proteinuria. He was re-examined September 1946 and May 1947 and seemed entirely well both times.

Case 17. L.S. This is another boy who survived as severe an infection as we have seen in a nephrotic patient. Both infection and nephrosis ended in complete recovery. The boy was 11 years old when brought to the hospital because of edema and vomiting. Results of laboratory studies are summarized in Table III. On the 20th hospital day he developed fever of 39.3°C. Ascites was marked and abdominal paracentesis was performed. The wound continued draining for the next five days and became infected. On the 29th day in the hospital the temperature rose to 39.6°C. and continued rising until it reached 40.7°C. A septic type of fever curve then persisted for the next 40 days, accompanied by episodes of coma and convulsions and the formation of multiple lung abscesses. Blood culture revealed hemolytic Staph. aureus. Sulfanilamide and sulfathiazole both proved ineffective. Penicillin was then obtained and a total of 500,000 units was given intramuscularly. Subsequently blood culture showed no growth and the boy recovered. During the course of this very stormy illness he lost all his edema; his body weight decreased from 54 kg. on admission to a low of 29 kg. He was sent home after 84 days. Examination one month later revealed no evidence of nephrosis. His weight at that time was 38 kg. Six months later he

still was well and weighed 43 kg. In May 1947 he weighed 56 kg., was in excellent health and had not had any recurrence of edema since recovery from his illness in 1944.

Case 15. W.P. This seven-year-old boy was the only child in whom mercupurin produced temporary hematuria. Admitted in May 1940, he presented the typical clinical and biochemical findings of nephrosis. He had several remissions and exacerbations of edema. In June anuria occurred; he was given 1 ml. of mercupurin intravenously, 6 ml. of a 25% solution magnesium sulfate intramuscularly and 25 ml. of 25% sucrose intravenously. One-half hour later gross hematuria occurred; 120 ml. of urine was passed. Now, seven years later he is in excellent health.

Case 20. G.S. This case appears to corroborate our impression that any treatment of nephrosis

TABLE III

BLOOD FINDINGS OF L.S. (CASE 17), 11 YEARS OLD, WITH SEVERE FEBRILE ILLNESS FOR 40 DAYS

Date *1943*	Plasma Protein, gm./100 ml.				Non-protein Nitrogen mg./100 ml.	Plasma Lipids, mg./100 ml.		
	Total	Alb.	Glob.	Fibr.		Total	Chol.	Lipid P.
12-2	3.6	0.9	2.2	0.5	61	1547	511	20.2
12-9	4.4	0.9	2.9	0.6	71	1480	636	17.5
12-17	4.1	0.9	2.7	0.5	67	2410	555	20.7
1944								
1-4	4.2	0.8	2.9	0.5	76	—	—	—
1-11	4.8	1.2	3.1	0.6	30	912	404	12.4
2-7	8.4	3.0	4.8	0.6	40	—	248	7.2
3-24	7.8	4.2	3.1	0.5	25	677	248	10.8
9-25	6.7	3.1	3.3	0.3	33	561	124	9.4

TABLE IV

BLOOD STUDIES OF PATIENT G.S. (CASE 20), 15 MONTHS OLD

Date *1942*	Weight kg.	Plasma Protein, gm./100 ml.				Non-protein Nitrogen mg./100 ml.	Cholesterol mg./100 ml.
		Total	Alb.	Glob.	Fibr.		
11-2	11.0	5.1	1.8	3.3	—	47	358
11-10	10.0	6.2	1.5	4.3	0.4	34	350
11-19	9.75	7.3	4.9	2.0	0.4	44	286
11-26	9.0	Sent home.					

is most effective when started soon after the onset of symptoms. Eight days prior to admission this boy became ill with irritability, anorexia, vomiting and rapidly increasing edema. He had had draining ears for three weeks. Admitted to the hospital he had severe edema, ascites and otitis media. Results of blood studies are shown in Table IV. Treatment consisted of a good level of environmental care, including a high protein, low fat complete diet given in small frequent feedings, ammonium chloride orally and blood and plasma transfusions. A week later edema was rapidly decreasing. In three weeks edema and proteinuria had disappeared. He has had no recurrence since.

Case 21. B.S. Two weeks prior to admission this girl developed proteinuria and puffiness of the eyelids. She was 16 months old when first seen. She weighed 10 kg. She had ascites and the edema was so severe that it closed the eyelids completely. Much mucopurulent nasal discharge was present. There was proteinuria without hematuria. She received large amounts of acacia intra-

venously, which produced violent vomiting. Edema showed many remissions and exacerbations. Eight months later she seemed well and was free from proteinuria. She remained well until six years later, when a severe upper respiratory infection with sore throat resulted in recurrence of edema, ascites and proteinuria. She was brought to the hospital critically ill. She weighed 28 kg.; she was cyanotic, dyspneic and severely edematous. The blood pressure was 115/75 mm. Hg. Roentgenograms revealed sinusitis. She was treated with frequent plasma transfusions, but edema increased further. Two months later she developed fever, leukocytosis, pain in the right lower quadrant of the abdomen, with localized tenderness over the appendiceal region. Appendectomy was performed. The appendix proved to be normal; the mesenteric lymph nodes were very much enlarged as was also the liver, which felt firmer than normal. The peritoneum over the mesenteric nodes appeared stippled. In retrospect this episode undoubtedly was a nephrotic crisis. We have seen other children in whom abdominal tenderness, a dominant symptom of these crises, was suspiciously localized over the appendix region, making differential diagnosis difficult. The girl under discussion was dismissed as recovered in November 1940 after several exacerbations and remissions. In 1941 there were a few episodes of edema, each time after upper respiratory infection. No edema has been present since 1942. In May 1947 she weighed 62 kg. and was found to be in excellent health; urine examination was negative; she was in the eighth grade at school and doing well. Menarche had occurred in 1945 and periods had been regular. This is the only instance in which we have observed a recurrence after a free interval of several years.

Case 22. G. T. This boy is the only child in the series who had gross hematuria, yet had no signs or symptoms of chronic nephritis at any time and is well today, 12 years after the onset of illness. The first evidence of illness was edema of the eyelids observed in June 1935. His urine was dark for three weeks; a physician found blood in it. On admission to the hospital he was extremely edematous and irritable. Blood pressure was normal. Liver and spleen could not be felt. Roentgenograms showed bilateral maxillary sinusitis. He received many blood transfusions and there was much fluctuation of edema. In October the urine tested 3 plus positive to Meyer's test for blood. In November he was treated intensively with intravenous infusions of 50% sucrose, with temporarily good effect on the edema. Later he received thyroid, as much as 0.25 gm. a day, without any effect on the edema. In January 1936 a parotid abscess developed which eventually drained. Subsequently he lost much edema. In June he returned, again edematous and with enlargement of the liver. The blood pressure was 108/62 mm. Hg. In December the edema had subsided; the blood pressure was 105/64 mm. Hg. There were occasional red blood cells in the urine. In April 1937 he was hospitalized with acute mastoiditis. Marked ascites was present. Antrotomy was performed. In August an upper respiratory infection precipitated a new exacerbation of edema. In December the blood pressure was 106/75 mm. Hg. The liver was not enlarged. Protein output ranged up to 13 gm./l. In September 1939 edema again was severe. In January 1940 he appeared to be entirely well with a blood pressure of 110/75 mm. Hg. Since then he has been well and without recurrence. This course was certainly typical of nephrosis, yet hematuria was gross at onset and recurred once. The case of this boy is the one exception to the criteria for diagnosis stated at the beginning of this paper in that he had hematuria. We have found only one somewhat similar instance in the literature. In 1943 Schwartz et al[8] reported a boy who had hematuria and subsequently developed the nephrotic syndrome; later he died and at autopsy no lesions indicative of glomerular nephritis were found. During 4½ years of illness of our patient, until recovery in 1940, 50 blood chemical determinations were made, each consisting of analysis of proteins, fats and nonprotein nitrogen. A few of these data are summarized in Table V.

Case 26. R.W. In 1942, when 11 years old, this boy was ill with suppurative arthritis of the hip joint (hemolytic Staph. aureus). In July 1945 he was admitted to the hospital because of generalized edema, ascites and oliguria. Examination showed chronic osteomyelitis of the right femur, marked proteinuria, normal blood pressure and rales in the lungs. The liver was felt 8 cm. below the costal margin. There was no hematuria at any time. Amyloidosis was excluded by a congo red test. In September of the same year glycosuria was noted. After appropriate studies, diabetes was diagnosed. He was placed under the diabetic regimen as practiced by this clinic and has been well controlled ever since. In May 1946 he seemed clinically well, the liver was no longer enlarged, but proteinuria was still present. In May 1947 examination and laboratory studies showed him to have recovered from nephrosis (Table VI). It appeared as if the blood proteins increased after

TABLE V

SUMMARY OF BLOOD STUDIES OF G.T. (CASE 22), 3¼ YEARS OLD

Date *1935*	Plasma Protein, gm./100 ml.				Non-protein Nitrogen mg./100 ml.	Cholesterol mg./100 ml.	Cl. mg./100 ml.
	Total	Alb.	Glob.	Fibr.			
10-18	4.8	1.9	2.4	0.5	28	320	—
11-16	4.9	1.5	3.1	0.3	64	381	555
12-27	5.4	2.0	3.0	0.4	27	513	573
1936							
1-24	7.1	3.3	3.5	0.2	—	320	583
2-10	6.2	3.4	2.5	0.3	43	381	585
6-2	4.5	0.9	3.1	0.5	30	533	—
10-17	4.6	3.1	1.1	0.4	27	210	—
12-7	5.3	1.7	2.8	0.7	40	655	608
1937							
12-15	4.2	1.7	2.5	0.3	33	354	—
1938							
8-24	5.4	2.0	3.2	0.2	32	616	—
11-10	4.3	0.7	2.8	0.8	27	615	—
1939							
4-7	7.1	3.7	3.0	0.4	33	195	—
9-7	4.9	1.5	2.8	0.6	43	417	—
10-19	6.7	3.2	2.8	0.7	36	237	—
1940							
2-1	6.9	4.1	2.5	0.3	28	212	—
6-21	7.5	4.0	3.4	0.1	38	—	—
1941							
1-25	6.8	4.1	2.4	0.3	40	174	—

TABLE VI

SUMMARY OF BLOOD STUDIES OF R.W. (CASE 26), 16 YEARS OLD

Date *1945*	Plasma Protein, gm./100 ml.				Non-protein Nitrogen mg./100 ml.	Cholesterol mg./100 ml.
	Total	Alb.	Glob.	Fibr.		
8-20	3.7	0.7	2.3	0.7	35	436
9-11	3.3	0.8	2.9	—	27	439
10-2	3.6	0.6	1.2	0.8	—	570
			Diabetes Controlled			
11-1	4.9	2.1	1.8	1.0	—	400
1946						
5-15	5.9	2.9	2.0	1.0	34	315

the diabetes had been controlled. However, there is no way of proving that this increase was due to diabetic management. This seems to be the only case ever reported in which diabetes and nephrosis occurred together.

Laboratory Studies

Determinations of blood protein fractions, nonprotein nitrogen and cholesterol were made at regular intervals with the blood of all patients. With many, total lipids, lipid phosphorus, prothrombin time and sedimentation rate (Westergren) were also determined. Standard methods were used for all the above analyses.[4] A Kolmer test was made routinely and was negative in all instances. Urine analyses were done regularly and protein output was measured semi-quantitatively (Esbach's method). Ascitic fluid was analyzed in several instances. Tables and charts included in the case reports demonstrate some of the values obtained. The prothrombin time was not significantly altered. Calcium values were generally decreased conforming to reports in the literature. Most of the increase in the blood fats took place in the cholesterol fraction. Phospholipids tended to increase parallel with the cholesterol. A few extreme values were obtained. The highest values were a total fat of 5170 mg./100 ml. blood, cholesterol 1303 mg., and lipid

TABLE VII

Levels of Blood Proteins and Cholesterol After Recovery from Nephrosis

Pat.	Interval	Plasma Protein, gm./100 ml.				Cholesterol	Lecithin	Total Fat
		Total	Alb.	Glob.	Fibr.	mg./100 ml.		
J.E.	Well 2 yrs.	6.7	4.0	2.3	0.3	260	200	572
J.H.	Well 3 yrs.	7.5	4.5	2.8	0.3	242	180	517
L.H.	Well 1 yr.	6.1	3.7	1.9	0.5	250	—	482

phosphorus 45.5 mg. With few exceptions, esterification of the cholesterol was unimpaired.

Plasma proteins showed the typical lowering of albumin (lowest value 0.3 gm./100 ml. blood) with increase in globulin, generally accompanied by increase in fibrinogen. High globulin values may result in a high figure for total protein, rendering such a determination alone, without salting-out the individual protein fractions, often valueless. Electrophoretic analyses of the plasma of nine children were made at intervals during the course of the disease. In general the partition between albumin, fibrinogen and total globulin fractions confirmed the chemical analyses. These data, including partition of the various globulin fractions, will be reported and discussed separately.[5] Frequently subjects were observed to lose weight rapidly and become edema free with very low plasma albumin values and elevated cholesterol values. During recovery phases, the plasma albumin values increased as the plasma cholesterol values decreased. However, a few of the children with normal albumin values for more than a year after recovery still had slightly elevated cholesterol values (Table VII).

The blood findings discussed above are in general agreement with other reports in the literature. Lowenthal[6] reported four nephrotic children with cholesterol values between 400 and 500 mg./100 ml. blood in the absence of edema. Schwarz and Kohn[7] made similar observations. Gottfried, Steinman and Kramer[8] have recently reported numerous

blood values for 10 nephrotic children during the course of treatment. In general the findings of these authors corresponded with ours: serum albumin values were low, serum globulin often above the normal range, but less consistently so than was observed by us. Serum cholesterol and total lipid were greatly increased in Gottfried's series; six of the nine values reported for lipid phosphorous were above the normal range. The serum calcium values reported by Gottfried were often surprisingly low. We have not observed values below 6 mg./100 ml. in these children, but we have rarely determined serum calcium in time of crisis or very severe edema.

It has been found that one cannot speak of a critical edema level for albumin in nephrotic children. We have seen some children free from edema with albumin levels less than 1 gm. and others very edematous with values greater than 2 gm./100 ml. It is well to remember also that blood albumin determinations do not always reveal the true state of body protein depletion; Weech et al[9] have shown that tissue proteins may be used to replace greatly depleted plasma proteins. When, in experiments with dogs, the loss of protein from the circulation was compared with the total loss of protein from the body, it was found that only one-fifth of the total loss was from the circulation while four-fifths were from body tissues outside of the blood stream.

Fluctuations of nonprotein nitrogen were found to be much more common than is generally realized. Increased nonprotein nitrogen in the blood is not always an indication of renal damage, as has been pointed out by Metcoff and Stare.[10] In nephrosis high nonprotein nitrogen values depend, among other things, on urinary output, fluctuations in edema, espisodes of fever and infection and possibly increased protein catabolism due to the high protein diet fed to children with this disease. Transitory increases of nonprotein nitrogen, followed by normal values, have been observed frequently and are compatible with a diagnosis of nephrosis. The highest value we observed was 79 mg./100 ml.

During the past few years we have determined the erythrocyte sedimentation rate of nephrotic children by the Westergren method. The sedimentation rate was determined simultaneously with blood protein and fat determinations.

The erythrocyte sedimentation rate has been known to vary with disturbances of the protein fractions of the blood. An accelerating action of the fibrinogen and globulin components and an inhibitory action of the albumin fraction has been described by various investigators. The latter has been by far the more constant of our observations.* Return of the sedimentation rate and the plasma albumin to normal values generally occurred simultaneously (Charts II and III). Gray and Mitchell,[11] working with pure human albumin, were able to depress the sedimentation rate considerably when adding albumin to bloods with markedly increased sedimentation rates.

It is our impression that fluctuations of the sedimentation rate depend mainly on disturbances of the normal balance between the three protein fractions. This concept is in keeping with that of Gordon and Wardley[12] who contend that the sedimentation rate is not controlled by the absolute concentration of total plasma proteins nor their fractions, but that it is dependent on the inhibition of one fraction by the other.†

* The correlation coefficient is —.85 for 40 paired values of the sedimentation rate and the plasma albumin observed at different periods in the course of the disease of seven children.

† The correlation coefficient is .30 for 40 paired values of the sedimentation rate and the globulin fraction; and .38 for 38 paired values of the sedimentation rate and the fibrinogen fraction. The observations were made at different periods in the course of the disease of seven children.

TABLE VIII. ANALYSIS OF FATAL CASES

No. and Sex	Age Onset Yrs.	Duration (Months) (a)*	Hematuria (b)†	Treatment (c)‡	Anatomic Diagnosis (d)	Glomerular Changes (e)	Liver Changes (f)	Cause of Death and Remarks (g)
27. F.	4¼	3¼	0	No S No P.	Degen. renal tubules; thrombus in abdom. aorta; infarcts of kidneys	Essen. normal. Few moderately congested	Wt.: 950 gm. Moderate congestion; sl. cloudy swelling; few vacuolized nuclei; no fat infiltration	Infection, Thrombosis, Pneumococcic bacteremia§
28. M.	1¼	1¼	0	No S. No P. Sucrose often	Degen. renal tubules; cardiac hypertrophy; pulmon. thrombosis and infarcts; ascites	Essen. normal. Slight increase cellularity of tufts	Wt.: 450 gm. Extensive congestion; some atrophy and portal necrosis of cells	Cardiac failure Thrombosis§
29. M.	5¼	18	0	No S. No P. Sucrose	Degen. renal tubules; cardiac hypertrophy	Scattered lesions with inc. collagen framework, occas. adhesions: few crescents	Wt.: 1750 gm; generalized congestion. Only mod. glycogen content	Cardiac failure Expired suddenly §
30. M.	7¼	2¼	0	No S. No P. Sucrose	Degen. renal tubules; cerebral edema, hydrothorax; ascites	Essen. normal, except increased vascularity	Wt.: 1000 gm. Congestion	Cerebral edema§
31. F.	2¼	1¼	5–6 RBC few times	No S. No P. Acacia	Degen. renal tubules; acacia deposits; patent ductus art. and for. ovale; pulmonary edema and hydrothorax; ascites	None	Wt.: 750 gm; Fat stain negative. Extensive changes due to acacia	Pulmonary edema; died respiratory death. Had severe edema
32. F.	2¼	4	0	No S. No P. Acacia	No autopsy	—	—	Pulmonary congestion; died suddenly with hemorrhage fr. mouth
33. M.	4¼	5	0	S.	No autopsy	—	—	Infection; Esch. coli bacteremia
34. F.	6¼	30	0	No S. No P.	No autopsy (Died at home)	—	—	Infection and recurr. of nephrosis
35. M.	1¼	24	2–3 RBC occas.	S. P.	No autopsy	—	—	Cardiac failure?;§ Sudden death with cyanosis and symptoms of shock.
36. M.	10	10	0	No S. No P. Acacia	Degen. renal tubules; pulmonary collapse; acacia deposits; hydrothorax; ascites	Small amount fat in tufts. Otherwise normal	Wt.: 1870 gm. Changes due to acacia. Very little fat	Pneumonia and pulmonary collapse; atheromatosis§
37. M.	3¼	¼	0	No S. No P.	Degen. renal tubules; lob. pneumonia; peritonitis	Few hyalinized; few questionable adhesions between tuft and capsule	Wt.: 640 gm; histologically normal	Infection§
38. M.	6	72	4–5 RBC twice	No S. No P. Acacia	Degen. renal tubules; peritonitis; empyema; acacia deposits	Obliteration; crescent formation; adhesions; epithel. proliferation	Wt.: 1680 gm, congestion; occ. degeneration; changes due to acacia. Very little fat (Sudan III)	Infection; NPN, CO_2, Cl normal. Blood acacia: 0.198 mg/100 ml. Atheromatosis§
39. F.	7	10	Occ. RBC, var. times	S.	Degen. renal tubules; peritonitis; hemolyt. strep. bacteremia	—	Wt.: 1200 gm. Normal architecture	Infection, 7500 cc. of blood and plasma during 8 mo. Fever 40.0° C. to 41.0°C. for 1 mo.
40. M.	7	5	0	No S. No P.	Degen. renal tubules; peritonitis; pleuritis; pericarditis	Some adhesion tuft to capsule; thickening of tufts; infiltration with inflammatory cells	Wt.: 900 gm. Cells granular; minute fat droplets in some areas	Infection: Erysipeloid lesion present on thigh

* From onset of first symptoms to death.
† Red blood cells per high power field, centrifuged specimen.
‡ S.—Sulfonamides; P.—Penicillin. Treatment other than sulfonamides, penicillin, sucrose and acacia not recorded in this table.
§ Patient discussed in text.

It must be remembered also, as has been pointed out previously by Malmros and Blix[13] that in different diseases different factors may be responsible for changes in the sedimentation rate. In rheumatic fever the sedimentation rate is increased, but our electrophoretic studies show an entirely different distribution of the protein fractions.[14] In cases of nutritional edema we have seen total protein values below 2 gms./100 ml. with normal sedimentation rate.

While among laboratory procedures the determination of albumin and cholesterol are probably the most valuable test in following the clinical course of nephrosis, facilities to carry out such procedures are not always available to the practicing physician. If, therefore, it could be shown that the sedimentation rate is a reliable index of disease activity in cases of nephrosis, this simple laboratory test would be a valuable aid in following children with this disease.* The sedimentation rate was uniformly increased as long as the disease was active. It became normal with recovery.

Discussion of Fatal Cases and Necropsy Findings

Seven of the 14 children who died with nephrosis were six years old or older at the time of death and six were over six years at the onset of illness. This does not bear out the belief that children past the age of six have a good chance for spontaneous recovery. Eight of the 14 fatal cases were ill for only 6 months or less, 2 for 10 months, 2 for 18 months and 2 for 2 years. Only one boy died of infection after six years of illness. Table VIII presents a summary of the fatal cases. Some of the cases offering points of special interest will now be discussed.

Case 27. N.B. This girl ran the typical course of nephrosis with diffuse edema during nearly four months of illness. It was complicated by a pneumococcus bacteremia with high fever, and bronchopneumonia. Two weeks prior to death, she developed bilateral thrombophlebitis of the saphenous veins. This subsided, but one day before death both legs became extremely painful and cold and showed diffuse, purplish mottling of the skin. The blood pressure remained normal throughout her illness, the liver became enlarged, the urine contained much albumin, many casts and white blood cells but no red blood cells.

At autopsy, a large thrombus of apparently recent origin was found, attached irregularly to the intima of the abdominal aorta. It extended from the bifurcation of the iliac vessels for a distance of 5 cm. Small extensions from this thrombus passed off into the smaller arteries. There was no thrombosis of the inferior vena cava. There was no peritonitis. The kidneys showed changes typical of nephrotic tubular degeneration and several areas of various early stages of infarction, manifested by hemorrhage and necrosis; the liver was enlarged due to congestion.

Case 28. N.E. This is another occurrence of thrombosis which in this instance involved the pulmonary artery. The patient's illness was of very short duration. He became ill with edema and was noted to have become unusually quiet. During his short hospital stay, the boy made no progress. Two days before death, he developed circulatory failure, after infusion of 300 ml. of whole blood. He improved the following day, but expired 24 hours later. He had received large amounts of sucrose up to four days prior to death.

Autopsy revealed a small thrombus, partially occluding the right pulmonary artery; it was dry and friable and on section showed very early organization at one border, indicating that it was not a terminal event. There were three small areas of infarction at the base of the right lung. The heart weighed 60 gm.

The kidneys showed no essential pathologic changes in the glomeruli, but marked tubular degenera-

* From onset of first symptoms to death.
† Red blood cells per high power field, centrifuged specimen.
‡ Sulfanilamide, P = penicillin. Treatment other than sulfonamides, penicillin, sucrose and acacia not recorded in this table.

* The correlation coefficient is .71 for 39 paired values of the sedimentation rate and cholesterol. These data also show a highly significant association between the sedimentation rate and proteinuria, chi-square equals 26.50, degrees of freedom 1; and between sedimentation rate and the degree of edema chi-square equals 33.94.

tion with some though not marked fatty infiltration of the lumina and epithelium of Henle's loop and of the collecting tubules. Some of the convoluted tubular epithelium was loaded with "colloid" droplets, considered to be cytoplasmic degeneration products.

The thyroid presented an unusual picture in that colloid was remarkably scanty, pale and granular. Wolbach and Blackfan,[55] who found similar changes in two of their cases, have discussed the significance of these changes and interpreted them as a sign of functional exhaustion of the gland.

Case 29. M.J. This boy had nephrosis for nearly a year and a half before entering the Children's Hospital. He was moderately edematous on admission, had some ascites and normal blood pressure. Treatment consisted of blood transfusions and large amounts of sucrose intravenously. This treatment resulted in only temporary loss of edema. A few days after an infusion of sucrose which resulted in marked diuresis, he very suddenly went "limp," became cyanotic, developed oliguria and dyspnea and expired.

At autopsy, cardiac hypertrophy was found. The heart weighed 160 gm. The lungs were dry and crepitant. Large amounts of blood oozed from the liver. In addition to marked tubular degeneration, there were also scattered glomerular lesions, consisting of increase in collagen framework, occasional glomerular adhesions and a few crescents of organized glomerular exudate. The lesions appeared to be healing rather than actively progressing, and were interpreted by the pathologist as "inactive glomerular nephritis."

Case 30. R.S. This boy had continuous edema for two months after the onset of illness. On entrance to the hospital, he was severely edematous, with ascites and signs of pulmonary edema. The blood pressure was 100/58 mm. Hg. There was an erysipeloid lesion on the thigh. Temperature ranged between 38.8°C. and 40.5°C. During the six days of hospitalization, he became comatose, at times talking irrationally. Shortly before he died, bilateral, external strabismus was noted. Ascitic fluid obtained during life was milky and contained pus cells. Culture revealed streptococci and staphlococci. Postmortem examination confirmed the clinical impression of cerebral edema. The brain was very wet and weighed 1450 gm. The sulci were flattened. The kidneys showed typical tubular degeneration with vacuolization and colloid degeneration of the convoluted epithelium. There were large amounts of lipoid material in the tubular epithelium.

There were no signs of peritonitis. We have seen and known of other cases in which normal peritoneum was found in the presence of infected ascitic fluid. These findings support Hartmann's[38] concept of "peritonitis" in nephrosis. He regards such infections more as an infection of the ascitic fluid, resulting from passage of organisms from what otherwise may have been transitory and harmless bacteremia into an area where growth can take place rapidly and where walling off is impossible because of the large amounts of free fluid.

Little mention is made in the literature of the occurrence of cerebral edema. Although it is realized that it represents an infrequent complication, constant watch should be held for it during critical periods.

Cases 31. D.J. and 32. J.J. These two girls represent two of the four fatal cases in which the children had received acacia therapy and have been discussed by Dick et al,[35] of this clinic. Appreciable amounts of acacia were found by chemical analysis in the liver, with evidence by microscopic examination of deposits in the bone marrow, lymph nodes, kidneys, spleen and liver.

Case 35. D.M. This boy's sudden death puzzled us a great deal. Unfortunately, permission for autopsy was not granted. For one and one-half years, he followed the typical course of nephrosis. At one time, very shortly after a plasma transfusion was started, he became suddenly cyanotic, became "limp" and appeared to be in shock. The blood pressure fell to zero and he expired very suddenly. His death resembled that of M.J., discussed above. It occurred during a period of marked fluctuations in edema.

Acute cardiac dilatation, likely to take place during such times of marked shift in body fluids, is the most likely explanation for his death.

Case 36. D.O. This child was admitted in acute distress with severe edema, ascites, oliguria and dyspnea. The blood pressure was 125/75 mm. Hg. There was ethmoidal sinusitis. The laboratory studies are presented in Table IX. Treatment consisted of acacia intravenously (total of 792 gm.), ammonium chloride orally, repeated small blood transfusions and high protein diet.

He had many upper respiratory infections. Ascitic fluid, on one occasion, was very cloudy and contained pus cells. Culture, however, was negative for pathogens. Shortly before death, he had a

chill, temperature of 40.5°C. and physical signs of pneumonia. Pneumococcic antiserum was given without avail (this was in 1935) and the patient expired.

Autopsy revealed several points of interest. There were 2000 ml. of cloudy fluid in the thoracic cage resembling that found in the peritoneal cavity. Culture of the fluid was negative, although culture of the peritoneal fluid, as well as the blood, revealed presence of Str. viridans.

There were some atheromatous changes in the ascending aorta. Microscopic examination revealed these to consist of an increased number of fibroblasts and a few cholesterol crystals. Periaortic lymph nodes showed suppurative adenitis.

Aside from tubular changes typical for the nephrotic kidney, there was a rather notable infiltration of the interstitial tissues with chronic, inflammatory cells. Acacia was present in all sections, but deposits were most marked in the cortex.

TABLE IX

SUMMARY OF CHEMICAL FINDINGS OF D.O., 10 YEARS OLD

Date *1934*	Serum Protein, gm./100 ml.			Non-protein Nitrogen mg./100 ml.	Cholesterol mg./100	Cl. mg./100	Other Blood Findings per 100 ml.	Urine Protein gm./l.
	Total	Alb.	Glob.					
9-5	2.20	0.66	1.23	41	290	505	Ca 9.6 mg. P 5.1 mg.	—
10-20	1.12	0.50	0.62	—	380	620	CO_2 66 vol. %	3.5
11-7	1.70	0.61	1.09	57	136	580	Acacia 2.1	5.3
12-17	3.37	1.12	2.15	42	568	—	BMR −33	7.5
1935								
1-12	4.50	0.67	2.30	76	494	—	—	4.0
2-23	3.60	1.00	2.60	43	430	—	—	2.4
3-27	2.90	0.90	2.00	36	625	—	Ca 9.0 mg.	7.8
4-5	2.78	0.54	1.86	50	650	—	—	—

Case 38. D.S. The autopsy findings in this patient have been reported by Falkenstein and Jackson.[18] Considerable amounts of acacia were found in the parenchymatous tissues of the body years after its administration. The kidneys showed both tubular and marked glomerular changes.

COMMENTS ON POSTMORTEM FINDINGS

Thrombosis of large vessels, occurring in nephrosis has not been reported with any frequency. Aldrich[19] reported one case of thrombosis of the renal vein (autopsy) and one of the iliac veins (no autopsy). Schwarz et al[7] have reported the occurrence of thrombosis in the middle cerebral artery.

Thrombosis of the abdominal aorta in children is a rare event. In 1935, Rothstein[20] summarized the literature and could find only 123 cases with a ratio of two and one-half in females to one in males. Apparently, it occurs most frequently in cardiovascular diseases and infections.

Bacteremia and slowing of the circulation due to pressure exerted by edema fluid, may be causative factors for thrombosis. The high level of fibrinogen in the blood also may be a factor. Atheromatosis also possibly may play a part in the formation of thrombi. We have seen atheromatous changes, as mentioned above, and Lowenthal,[6] Schwarz and Kohn[7] and Dodd[21] have reported them. There was, however, no atheromatosis in the cases of thrombosis we have observed. Blood cholesterol was not particularly

high in one of the two children with atheromatosis and in the other it was lower than in many children who survived. Duration of illness in the two cases with atheromatous changes may be seen from Table VIII.

Because of striking paucity of reports on liver findings in autopsies of nephrotic children, special attention was given this organ. Marked fatty infiltration of the liver cells was not an outstanding feature (Table VIII). In the majority of cases, pathologic changes in the liver were inconspicuous, except for those cases in which acacia therapy was used. Wolbach and Blackfan[15] interpret the slight liver changes which they found in their material, as merely due to "overtaxed functional activity." Blackman[22] found fatty infiltration of the liver parallel to the amount of fat found in the kidneys.

Some investigators believe that nephrosis may be caused by disturbances of liver function. There is good clinical and patho-physiologic evidence for this. Histologic findings, however, failed to substantiate these theories.

There has been some discussion in the literature concerning the problem of anemia in nephrosis. In our series, anemia was exceptional and when it occurred, it was transitory and there were no difficulties in re-establishing normal blood values with transfusions. In one child (J.W.), the hemoglobin at one time decreased to 6.6 gm./100 ml. and the RBC to 2.7 million. Soon thereafter, however, normal blood values were again obtained. Episodes of infection may likely play a role in the temporary depression of the hemoglobin and red blood cell count. Bone marrow examinations revealed normal cytology and no signs of disturbed functional activity in eight samples examined at autopsy. In one, the marrow was hyperplastic. When acacia was given, it was found in phagocytes even in the bone marrow.

Glomerular involvement in lipoid nephrosis has long been a point of major controversy. A correlation between hematuria and glomerular changes found at necropsy, would, therefore, be of interest. Perusal of Table VIII will show that in only four or five cases could one possibly speak of microscopic hematuria. Minor glomerular changes were seen in the kidneys of four children not known to have had hematuria. Of the four children who did not show any glomerular changes, two had minimal hematuria on several occasions. Three children who had passed occasional red blood cells (but less than 10 per high power microscopic field) on various occasions, are today living and well.

More pronounced glomerular changes, diagnosed by the pathologist as subacute glomerular nephritis, occurred in two children, one of whom was never known to have red blood cells in the urine during two years of illness, while the other was known to have only four to five red blood cells in the urine on two occasions during six years of illness.

It is realized that microscopic hematuria occurs very sporadically, so that there may be times when urine examinations are not performed at the very moment hematuria takes place. However, these children were hospitalized so frequently and over such long periods of time that were hematuria present to any significant degree, it would have been found.

Our observations thus seem to indicate that there is little, if any, relationship between the degree of microscopic hematuria and permanent glomerular damage in lipoid nephrosis.

Like Davison and Salinger[23] and many other observers, we have seen glomerular and

interstitial changes—as described above—in typical cases of lipoid nephrosis fulfilling the strict criteria stated at the beginning of this paper.

The glomerular changes appear to be of minor significance in most instances. Some may perhaps be inflammatory reactions, occurring during periods of infections to which the nephrotic child is so susceptible. We like to believe that glomerular changes may become arrested (see Case 29) or may even be reversible (Case 22, Table I). However, in some instances, glomerular changes may progress sufficiently to give the picture of chronic nephritis, biochemically and histologically.

Clinically, however, such children do not resemble the patient with chronic nephritis. The clinical course of that disease, the presence of azotemia, hypertension, severe anemia, gross hematuria, retinopathy, impaired renal function, chronic acidosis and retardation of growth and development are all missing in the nephrotic child who eventually may show evidence of nitrogen retention and histologic lesions of chronic nephritis. For these reasons we believe that these children have not had chronic nephritis from the onset.

In addition to the children discussed above, two children have been studied whose illnesses were typical of nephrosis until the terminal phase of the disease, when evidence of chronic nephritis was observed. One boy (T.C.), entered the hospital at four years of age with symptoms typical of nephrosis. His serum albumin was 0.8 gm./100 ml. He remained in the hospital until his death 17 months later; during all this time he was never free of edema. The plasma albumin fluctuated from 0.8 to 1.5 gm./100 ml. nonprotein nitrogen from 35 to 42 mg./100 ml.; plasma lipids were notably increased; the maximum values observed were total lipids 5170 mg./100 ml., lecithin 1070 mg., total cholesterol 1180 mg./100 ml. He developed azotemia about six weeks before death. Blood values one week before death were nonprotein nitrogen 160 mg./100 ml., plasma cholesterol 688 mg., plasma protein 4.8 gm., albumin 1.4 gm./100 ml.

Another boy (E.S.), four years old at onset, was observed for 19 months, until he died. For over a year, his clinical course and the biochemical data were unequivocally typical of nephrosis. The plasma albumin varied from 0.6 to 1.8 gm., the nonprotein nitrogen from 35 to 40 mg./100 ml. and cholesterol from 480 to 1002 mg./100 ml. He then began to show persistently high nonprotein nitrogen values and a little later moderate but persistent hypertension was recorded. He died during an acute exacerbation of his disease, manifested by severe generalized and pulmonary edema. Autopsy permission could not be obtained. He, too, was excluded from this series.

In view of such observations, one should keep in mind when discussing the prognosis of a nephrotic child, that nephrosis at times may terminate as nephritis, with persistent azotemia and fatal outcome. Often, it may take many months before a verdict can be reached whether a given case will remain one of lipoid nephrosis or if signs of chronic nephritis are developing.

These observations are in accordance with those of Blackman[24] who has given careful consideration to the question of a relationship between nephrosis and nephritis. It seems that so long as the cause of nephrosis remains obscure, one should not be dogmatic one way or the other when discussing the nephrosis-nephritis problem.

Treatment

The management of nephrotic children has recently been discussed by Kobayashi[25] of this clinic.

We have experimented with a host of remedies, including the vitamins B, C, and E, but have found none of specific value. Diuretics may be useful to give relief to the severely edematous child. Concentrated salt-free serum albumin will likely prove itself to be the most effective diuretic, but it seems doubtful whether it is more than just that. Consequences as described above, have made us become very hesitant in the administration of sucrose. When used, it should not be given in such quantities as to bring about sudden and rapid diuresis, because of the danger of resultant circulatory failure. It should be administered at a slow rate and blood pressure, pulse and respirations should be checked at short intervals. We have seen instances of spectacular diuresis after sucrose infusions, but improvement in most cases was temporary only.

Since disturbance of fat metabolism is such an outstanding feature of the disease and in view of rather frequent enlargement of the liver, it was thought that choline might prove helpful. Choline citrate, 0.8 gm. per day, was therefore given to seven children over long periods of time.* In some instances, it was incorporated into an elixir of vitamin B complex. Detailed biochemical studies were made on these children. The results were discouraging and will, therefore, be mentioned only briefly.

Unequivocal improvement did not occur in any instance. Three of the children are well, two of the children died, and two still have active disease. A consistent and significant increase in blood fats, after choline administration, was not observed. The results obtained by Major[26] could not be duplicated. He reported a preliminary rise in cholesterol followed by a gradual fall. The dosage of choline, however, was bigger in Major's cases since 3 gm. were given each day to each of five patients.

Failure to find marked fatty infiltration of the liver may account to a certain extent for our negative results.

Acacia therapy has not been used in this clinic since Jackson et al[27] presented experimental evidence of liver damage and suppression of blood protein formation after infusion of this substance.

Some of the children who died had received very intensive treatment with large amounts of either blood, plasma or sucrose infusions. We have been wondering whether actual harm possibly may be done to the kidneys by such measures.

We also gained the impression that periods of sudden change in edema are critical times for the nephrotic child. Therapeutic procedures at such times should be performed with much care.

In two children we have tried to lower the blood cholesterol by giving bile salts by mouth, hoping to increase the flow of bile and thus the cholesterol output. Stool analyses failed to show an increased cholesterol output and blood levels did not fall.

The "curative" effect of intercurrent infections has been widely discussed in the literature. There is no doubt that various infections have materially contributed to recovery in some of our cases. Among the infectious diseases, measles has played a prominent part. The latest report on the effect of measles on nephrosis, containing extensive references on the subject, came from Blumberg and Cassady.[28] In most instances, periods of observation have been too short to be certain whether recovery will be permanent. If temporary recrudescence only is obtained, it seems that the risk involved

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* Choline preparations were supplied through the courtesy of Dr. T. H. Jukes, Lederle Laboratories, New York.

in giving measles voluntarily to nephrotic children, would not be worth the effect obtained.

It is our clinical impression that any form of treatment is most effective when the patient can be treated very shortly after the onset of first symptoms. Therefore, we suggest that any child with edema and proteinuria be hospitalized at once for diagnosis and for treatment if nephrosis is present. Although no treatment has proved specific, intensive therapy including close nutritional supervision, transfusions and paracentesis may result in a rapid recovery if instituted early in the course of the disease.

Summary

Clinical and biochemical studies of 40 children with lipoid nephrosis are evaluated. Twenty-six (65 %) are alive; 19 have been entirely well for 1 to 16 years, including three who had minimal hematuria on various occasions. Three have been well for less than a year, one still has proteinuria only, and three still have active disease. Of 22 children who had received sulfonamides for infections, only three have died. Necropsy was done on 10 of the 14 children who died. Minor glomerular changes were seen in the kidneys of four children not known to have had hematuria. Pronounced glomerular changes occurred in two children who had minimal hematuria. Of the four children who did not show any glomerular changes, two had minimal hematuria on several occasions. Pathologic changes in the liver were minimal unless acacia had been given.

Laboratory determinations revealed no significant alteration of the prothrombin time. Most of the increase in the plasma fats was in the cholesterol fraction. The precentage of cholesterol esters was not decreased. In case of recovery, the cholesterol seemed to return to normal values at a slower rate than the serum albumin. Plasma fat reached values exceeding 5 gm./100 ml. in some instances. No "critical edema level" for albumin was found. The erythrocyte sedimentation test was a reliable guide in determining the course of the disease.

Choline citrate (0.8 gm. each day), given to seven children for prolonged periods, failed to produce essential changes in the plasma fats or definite clinical improvement.

Periods of sudden change in edema were found to be critical times for the nephrotic child. Two children developed cardiac failure after injection of large volumes of sucrose.

Early diagnosis is important, for treatment is most effective in the early stage.

The prognosis is good since the advent of chemo- and antibiotic therapy, and is not impaired by prolonged duration of the disease. Growth of the children who recover is good.

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SPANISH ABSTRACT

Nefrosis Lipoidica; Estudio Clinico y Bioquimico de 40 Niños, con 10 Necropsias

Se estudian desde el punto de vista clinico y bioquimico cuarenta niños con nefrosis lipoidica. Veintiseis, (65%) estan vivos; diez y nueve de ellos completamente bien, de 1 a 16 años, incluyendo tres que han tenido muy pequeñas hematurias en varias ocasiones. Tres han estado bien por menos de uno año, uno tiene todavia solamente proteinuria, y tres tienen todavia la enfermedad activa. De los 22 niños que han recibido sulfas por infecciones, solamente tres han muerto. La necropsia fue hecha en diez de los catorce niños que murieron. Pequeños cambios glomerulares fueron observados en los riñones en cuatro niños, no se sabe si tuvieron hematuria. Marcados cambios glomerulares se observaron en dos niños que tuvieron pequeñas hematurias. De cuatro niños que no mostraron ninguna alteracion glomerular, dos tuvieron hematuria minima en varias ocasiones. Cambios patologicos en el higado fueron pequeños, á menos que se habia usado acasia.

Los examenes de laboratorio no revelaron marcadas alteraciones del tiempo de protrombina.

Muchos de los aumentos de la grasa en el plasma fue a expensas de la fraccion colesterol. El percentaje de colesterol no fue disminuido. En casos de curacion el colesterol retorno a los valores normales mas lentamente que la albumina del suero. La grasa del plasma alcanzo valores excelentes a 5 gm./100 ml. en algunas ocasiones. El nivel critico de las albuminas para el edema fue encontrado. La prueba de la eritrosedimentacion fue realmente una guia en la determinacion del curso de la enfermedad.

El citrato de colina (0.8 gm. cada dia) se administro a siete niños durante periodos prolongados, sin que se produjeran esenciales cambios en la grasa del plasma ni definitivas mejorias clinicas.

Periodos de cambio rapido en el edema fueron encontrados ser los momentos criticos del niño nefrotico. Dos niños desarrollaron falta cardiaca despues de la inyeccion de grandes cantidades de sucrosa.

El diagnostico temprano es muy importante, porque el tratamiento es mas efectivo en los primeros estadios.

El pronostico se ha hecho bueno desde el advenimiento de la terapeutica antibiotica y quimica sin importar la prolongada duracion de la enfermedad. El crecimiento de los niños que curan, se hace bien.

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ACUTE ATAXIA IN A TWENTY-MONTH-OLD FEMALE

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THE remarkable diversity of clinical manifestations which may be produced by the encephalitides is well known, and accurate descriptions of various forms are included in the more extensive neurologic treatises, as well as in large numbers of case reports. In general, however, more or less distinct forms have prevailed during specific epidemics, and even in sporadic cases occurring in consecutive years. The case herein reported differs substantially from the great majority of clinical syndromes included under the usual descriptions of encephalitis, and in particular is reminiscent of unusual manifestations recorded in certain geographic areas during the epidemic of the years 1917-1921.[1-2] Still other manifestations are similar to those exhibited in a group of patients reported by Dubini in 1846,[3] and later elaborated upon in a group of children studied by Bergeron[4] in 1880. Griffith[5] has described 17 cases of what he termed cerebro-cerebellar ataxic form of encephalitis, some of the signs of which were present in our patient. More recently, the group of seven children reported by Klingman and Hodges[6] as acute cerebellar ataxia of unknown origin showed pronounced features in common with the following case.

CASE REPORT

H.M., a 20-month-old female infant of Albanian parentage, was admitted with the complaint of staggering gait, jerky movements of the head and all extremities, of 18 days' duration.

The infant was born after an uncomplicated full term pregnancy and delivery. The neonatal period and subsequent development and course were normal. One sibling aged four was alive and well, as were both parents. There were no significant diseases in the family.

Eighteen days prior to admission, without preceding illness of any sort, the patient was noted to have a wobbling extremely unsteady gait, and fell frequently to either side. At the same time, jerky movements of the head from side to side were observed, in addition to rapid irregular movements of the eyes in all directions. Shortly after the onset the patient was hospitalized elsewhere and spinal fluid and skull X-rays were reported to have been negative. The symptoms continued unabated until three days prior to admission when the picture became exaggerated, the child slept hardly at all, and the extremities, trunk, head and eyes were in a state of almost perpetual motion. These movements lessened during sleep, but at no time did they entirely disappear. There had been no fever, or convulsions, the appetite had remained good, swallowing was apparently unimpaired, and no mental changes had become evident. There was no history of head trauma, exposure to contagious disease, ingestion of lead-containing substances or of drugs.

Physical examination showed a well developed and well nourished infant who did not appear acutely or chronically ill. She responded to simple commands, and spoke a few unintelligible words. Very striking were the numerous spontaneous movements throughout the entire body, and in particular those of the eyes and chin. At times there was a rhythmic tremor, suggestive of pill rolling, of the fingers of the left hand. Any change of the motor setting, such as an intention, made the movements more conspicuous. For example, on attempting ocular fixation of any object at near point the head jerked from side to side, and occasionally nodding movements were present. Under fixation, the ocular movements were irregular, lightning-like, and often had a torsion component. These movements were completely dissociated. Thus, one eye would move outward, while the other would move upward and outward.

All types of visual stimuli suddenly introduced were usually accompanied by a startle reaction of

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the body, including the head and eyes. Under these circumstances the ocular movements became rapid, zig-zag, irregular, and were associated with torsion-like spasms of several seconds' duration. Auditory stimuli suddenly introduced also produced a generalized startle reaction, but not nearly to the degree produced by visual stimulation, such as the sudden flashing of a bright light. The pupils were equal, reacted to light and on accommodation, and the fundi, examined under anesthesia, were normal.

In the attempt to reach for an object, ataxia of the hands was clearly evident. The infant could stand with support, but walking was almost impossible, the lower extremities being held stiffly, though there was no spasticity, or any other variety of hypertonus. If the patient was supported by the hands in standing position, her attempts at walking resulted in a very broad-based gait, the legs were held hyperextended and were circumducted in her attempts at a few steps.

Sensibility to pain may have been impaired generally, since varying stimuli seemed to provoke mild facial expressions of pain, though on no occasion did the patient react by withdrawal. The deep tendon reflexes were equal, and normally active, and there was no ankle clonus. An inconstant Babinski sign was present on the left.

The patient was observed several times while asleep, during which all previously described abnormal movements were still present, but to a much lesser degree than during waking hours. Conspicuous during sleep were champing and sucking movements, and not infrequently the lids were seen to be undergoing arrhythmic contractions. When awakened gently the infant would arise with a sharp cry; there was no startle reaction, but the eyes manifested the dyskinesias as previously noted.

The general physical examination revealed no abnormalities.

Laboratory: Hemoglobin was 14 gm./100 cc. blood; WBC was 8.8, with 48% polynuclear leukocytes, 48% lymphocytes, 2% monocytes and 2% eosinophiles. The urine was normal. Lumbar puncture revealed faintly pinkish fluid under normal pressure. Fresh RBC—100/cc., and lymphocytes—6/cc.; Pandy—negative; total protein—50 mg./100 cc. fluid; sugar—70 mg./100 cc.; Wassermann and colloidal gold tests—negative. The blood Wassermann reaction was negative. Roentgen examination of the skull—normal. Pneumoencephalogram performed two months following onset of illness was reported as possibly showing a slight amount of cortical atrophy. No definite abnormality of the ventricular system was demonstrated. Electroencephalogram suggested a diffuse process, with the greatest concentration in the mesencephalon.

Course: Under treatment with phenobarbital in dosage of 0.015 gm. four times daily the patient showed marked improvement during the first two weeks of hospitalization, to the point where there were only very few of the spontaneous movements previously described, and none during sleep. Nystagmus in all directions was still present when the child tried to follow objects, but the torsion movements had disappeared. The intention tremors had lessened considerably, but ataxia remained so marked that walking without support was impossible. The child was discharged after a 13 week hospitalization, but returned again five weeks later and remained for a period of 3½ months. On readmission her condition appeared to be about the same, improved in some respects, i.e., she could occasionally reach for objects without evidencing ataxia, worse in that she now had developed a fixed internal strabismus on the right. She spoke a few words which were just intelligible, was very responsive, and intelligence did not appear to be impaired. Marked emotional reactions attended lack of attention, the infant screaming violently and exhibiting increased abnormal movements, if any of the nurses or doctors who had been attending her left suddenly. Return to the side of the patient resulted at once in cessation of screaming and marked diminution of the abnormal movements. Startle reactions could still be elicited, but these were minimal, and stimuli had to be much stronger than previously. No further essential change became apparent in the 3½ months of hospitalization.

Comment

Although the absence of abnormal spinal fluid findings and of fever at any time immediately preceding or during the course would seem to be against the diagnosis of an encephalitis, nevertheless the abrupt onset in a previously perfectly healthy infant, of a symptom complex indicating rather extensive involvement of the brain, without evidence of degenerative stigmata, trauma, intoxications, tumors, congenital anomalies

or vascular lesions, points to an encephalitis. The course of the disease in the six months, during which the patient was observed, also suggests an encephalitic process, with some of the sequelae occasionally seen in children.

In reference to the presence of several unusual manifestations occurring in the same patient, all of these have previously been described in cases of encephalitis, as occurring either singly or in a variety of combinations. The remarkable involvement of the eye movements, i.e. the irregular, lightening-like, completely dissociated movements of the eyes, together with the dramatic startle reactions produced by visual stimuli, suggest in this instance a much more marked mesencephalic involvement than is usually seen. The lightning-like movements, occurring suddenly as if produced by an electric stimulus, correspond closely with those signs described by Dubini and Bergeron[4] whose names have been applied to the very descriptive term "electric chorea." The myoclonic variety of epidemic encephalitis (encephalitis algomyoclonica) was frequently described in 1920, and appears to have been a representation of the quick jerky movements which our patient showed. The children described by Griffith[5] under the term cerebro-cerebellar ataxia, with predominantly cerebellar involvement, had had one of the acute infectious diseases just prior to the nervous system manifestations in all but two instances. The seven children, aged 2 to 4½ years, studied by Klingman and Hodges[6] all had an abrupt onset of ataxia, intention tremors of the extremities, marked muscular incoordination, and speech difficulties. One of this group showed myoclonic movements, two evidenced nystagmus, and only two had spinal fluid abnormalities represented by a slight increase in the number of lymphocytes; 16 in one case, and 20 in another. Five of this group made complete recoveries in periods ranging from 1 to 14 months. One showed a marked behavior disturbance beginning 39 days after the onset of the disease, and had eventually to be institutionalized. The last patient still showed impairment of coordination seven months after onset. The authors were unable to conclude that they were dealing with a true encephalitis, or an acute non-suppurative disturbance of the nervous system. However, the type of onset, manifestations, and course of their patients suggest an encephalitis rather than other conditions which might simulate the syndrome which they described, i.e., acute infections, trauma, intoxications, tumors, or vascular lesions.

Hunt[7-8] described a similar symptom complex but of progressive or chronic nature, under the designation *dyssinergia cerebellaris progressiva* and *dyssinergia cerebellaris mycolonica*. He felt that these resulted from a primary system disease of the cerebellum and its efferent pathways, the dentate system. The causative factor was thought to be a primary atrophic process, and this seemed to be borne out by pathologic studies in one case. Our patient, although she showed similar manifestations to those described by Hunt, nevertheless gave evidence of severe midbrain disease with probable involvement of such structures as the red nucleus, reticular formation, and brachium conjunctivum. In addition, she showed definite improvement during the first two weeks of hospitalization, and she appeared to be unchanged thereafter except for the development of marked emotional instability. If anything, there seemed to be a lessening of the tremors at rest, and improved ability to control voluntary acts.

Summary

A case of probable encephalitis in a 20-month-old female infant with bizarre manifestations pointing primarily to involment of the mesencephalon and cerebellum is

described. Similarities to the so-called electric chorea of Dubini and Bergeron, the myoclonic and the acute cerebellar forms of encephalitis are discussed.

ACKNOWLEDGEMENT

The authors are indebted to Dr. Morris Bender of the Mount Sinai Hospital Neurologic Service for his advice and interest in the elucidation of this case.

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SPANISH ABSTRACT

Ataxia Aguda En Una Niña De 22 Meses

Un caso de ataxia de comienzo subito en una niña de 22 meses fue observado durante un periodo de seis meses. Encefalitis fue el diagnostico planteado. Tenia raras manifestaciones afectando particularmente los ojos, raras reacciones espantas y generalizadas con los estimulos visuales y auditivos. Alguna similaridad con la corea electrica de Dubini y Berjeron y con la forma mioclonia cerebral aguda de la encefalitis son presentadas. El unico cambio significativo aparecido en la paciente en los seis meses de observacion fue alguna mejoria en la coordinacion y gradual desarrollo de una reaccion explosiva emocional en respuesta de la prueba de la luz, falta de interes evidenciado por las personas del Hospital. La inteligencia no parece afectada por la enfermedad.

888 Park Avenue

FORMULA ROOMS FOR NEWBORN INFANTS IN LYING-IN HOSPITALS

A Preliminary Study on Supervision and Certain Technics for Preparation

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IT IS now generally agreed that the care given to formula preparation is of paramount importance in the prevention of the spread of infection, particularly the diarrheal disorders, among newborn babies in hospital nurseries.[1, 2] Until recently formulas for newborn infants have usually been prepared in almost any available section of the hospital—diet kitchens, pantries and closets. Methods of formula preparation have varied and the factor of safety has been largely overlooked. It is only within the past few years that standards designed to promote more satisfactory methods have been devised. Likewise only recently has it been realized that the problem requires further study.

In connection with our program of supervision of maternity hospitals,[3-5] we have been interested in the problems presented by formula preparation and believe that our experience may be of interest to others currently working with newborn babies. What type of personnel staff the formula room suites and what degree of supervision is present? What are the various technics employed? How safe are the final products as determined by bacteriologic studies? In this communication we are presenting answers to simple questions concerning staff and supervision, and technics such as terminal sterilization of formulas.

HOSPITALS SURVEYED

The formula room procedures of 113 hospitals giving lying-in care were studied. Only observations made during the past year were analyzed. With five exceptions, all hospitals have other general services aside from the maternity and newborn. Somewhat over one-half (55%) have a capacity of 20 to 49 maternity beds. Less than one-quarter (20.3%) have a capacity of under 20 maternity beds and the remainder (24.7%) a capacity of 50 beds and over (Table I).

RESULTS OF SURVEY

Supervision of Formula Rooms

1. Type of Supervisor—Of the 113 hospitals surveyed, 39 (34%) assigned either a graduate nurse or trained dietician to supervise the technics used by the personnel in the preparation of formulas (Table II). The remaining 74 hospitals (86%) provided no supervision. Of these 74 hospitals, 63 had a capacity of fewer than 50 beds. It appears that the larger maternity services had more supervision.

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2. Time Given by Supervisor—From the point of view of efficiency and economy, it seemed desirable to study the amount of time actually spent by the supervisor in the management of the formula room. Only two of the 39 hospitals providing formula room supervision had daily supervision during the entire period of formula preparation. In these two hospitals one had a graduate nurse in charge and the other a dietician. The

TABLE I

DISTRIBUTION OF MATERNITY BED CAPACITY

Number of Maternity Beds	Number of Hospitals	Percent of Hospitals
Under 20	23	20.3
20–49	62	55.0
50–79	19	16.8
80–109	5	4.4
110 and over	4	3.5
Totals	113	100.0

TABLE II

TYPE OF SUPERVISOR IN FORMULA ROOMS
Number of Hospitals

Number of Maternity Beds	Graduate Nurse	Dietician	None	Total	Percent of Total with Supervision
Under 20	0	0	23	23	0.0
20– 49	20	2	40	62	35.5
50– 79	3	5	11	19	42.1
80–109	3	2	0	5	100.0
110 and over	3	1	0	4	100.0
Totals	29	10	74	113	34.5

remaining 37 hospitals gave irregular supervision at such times available to the supervisor whose additional duties took her to other parts of the hospital.

Personnel Working in Formula Rooms

1. Type of Personnel—Of the 113 hospitals, 41 had graduate nurses in the formula rooms, and 52 had attendants only. Of the 23 hospitals having less than 20 maternity beds, 16 had an attendant in charge (Table III). An attempt was made to correlate the type of personnel working in the formula room with the question of supervision. It was found that the 23 hospitals having fewer than 20 maternity beds had no supervision of the formula room and two-thirds of these hospitals had only an attendant working there. Of the 62 hospitals having 20 to 49 maternity beds, 40 had

no supervision of the formula room, and approximately one-half of these employed only an attendant. Of the 19 hospitals having 50 to 79 maternity beds, 11 had no supervision and approximately one-half of these employed only an attendant in the formula room.

TABLE III

TYPE OF PERSONNEL ACTUALLY PREPARING FORMULAS

Number of Maternity Beds	Gradu- Nurse Only	Gradu- ate and Student Nurse	Gradu- ate Nurse and Attend- ant*	Student Nurse Only	Stutent Nurse and Attend- ant*	Attend- ant* Only	Die- tician Only	Total Number
Under 20	7	0	0	0	0	16	0	23
20– 49	20	3	2	5	2	26	4	62
50– 79	6	0	0	4	0	8	1	19
80–109	1	1	0	2	0	1	0	5
110 and over	1	0	0	1	1	1	0	4
Totals	35	4	2	12	3	52	5	113

* The term attendant here refers to aides, baby nurses, licensed and unlicensed practical nurses.

TABLE IV

AMOUNT OF DAILY TIME DEVOTED BY PERSONNEL IN ACTUAL PREPARATION OF FORMULAS

Number of Maternity Beds	Daily Full-time Assignment	Daily Partial Assignment	Total	Percent of Total with Full-time Personnel
Under 20	0	23	23	0.0
20– 49	10	52	62	16.1
50– 79	9	10	19	47.4
80–109	5	0	5	100.0
110 and over	3	1	4	75.0
Totals	27	86	113	24.0

2. Time Devoted by Personnel in Formula Room—As was to expected less time was required in formula preparation in hospitals with smaller obstetric services (Table IV). Apparently, in these hospitals the tendency is to assign inexperienced or untrained personnel to this procedure. As in the past, formula preparation is still being looked upon by many as an auxiliary service which does not require the assignment of a skillful person.

Of the 113 hospitals, 27 (24%) had personnel that devoted full time to the

formula room and 86 (76%) had the same individuals assigned to other additional work on the maternity and newborn service. All hospitals having fewer than 20 maternity beds and most hospitals having 20 to 49 maternity beds had part-time personnel in the formula room.

Method of Terminal Handling of Formula

Of the 113 hospitals, only 30 (27%) used some type of terminal processing of the formula either by an autoclave or by pasteurizer. Eighty-three hospitals (73%)

TABLE V

METHOD OF TERMINAL HANDLING OF FORMULAS

Number of Maternity Beds	Terminal Processing		No Terminal Processing		Total	Percent of Total With Terminal Sterilization
	Formula Poured; Nippled and Nipple Capped; Autoclaved	Formula Poured; Nippled and Nipple Capped; "Pasteurized"	Formula Poured; Nippled and Nipple Capped; No Terminal Processing	Formula Poured; Rubber Capped; Nipple Applied in Nursery; No Terminal Processing		
Under 20	1	1	20	1	23	8.7
20– 49	8	10	33	11	62	29.0
50– 79	1	5	12	1	19	31.6
80–109	0	1	3	1	5	20.0
110 and over	0	3	1	0	4	75.0
Totals	10	20	69	14	113	26.6

made no attempt at terminal sterilization. It should be noted that all hospitals, with the exception of two, having fewer than 20 maternity beds fell into this group (Table V). This finding is significant in light of the little supervision in these hospitals.

Terminal Sterilization of the Final Formula Product

The question whether the final formula after pouring, nippling and nipple-capping of the bottle should receive some type of terminal sterilization is one that is now being considered by pediatricians, hospital administrators, and public health workers. It was therefore thought advisable to review the literature and to secure a cross-section of prevailing opinions from authorities in these fields.

Review of the Literature

The literature for the past 15 years was searched and the results are given in Table VI. Ten investigators favored terminal sterilization by steam under pressure; two favored terminal sterilization by non-pressure steam, and two favored terminal pasteurization. As far as we could ascertain, no references could be found on the

TABLE VI

METHOD RECOMMENDED FOR TERMINAL HANDLING OF FINAL FORMULA PRODUCT FROM REVIEW OF LITERATURE—1932 TO 1947

Author	Terminal Autoclaving at 121°C. for Approximately 10–15 minutes	Terminal Steam Sterilization at 76.7°–82.2°C. for Approximately 20–30 minutes	Terminal Pasteurization at 65.5°–68.3°C. for 30 minutes	Other Methods of Sterilization
Pattani and Harrington[6]	This method should be used			
C. P. Wright, Jr.[7]	This method is recommended			
Rourke[8,9]	This method for 10 minutes gives a completely sterile product	Feels this method is satisfactory. (But his data does not show that this method gives as good bacterial results as first method.)		
Gillam[10]	In her survey, this method is used by 37.3% of hospitals surveyed.	In her survey, this method is used by 44.6% of hospitals surveyed.		
Cummings[11]	Recommends this method for 8 minutes at 120°C.			
Sauer[12]	Recommends this method for 15 minutes at 15 lbs. pressure			
Traisman and Halpern[13]	Recommend this method			
Erikson and Sauer[14]	Recommend this method			
Weymuller[15]			Recommends this method. 60°–71.1°C. for 30 minutes	
Consolazio[16]	This method is recommended			
Merritt, et al.[17]			This method is used	
Lowe[18]	This method is recommended at either 104.4° or 110°C. for 5 min.			
Bergman[19]				Terminal autoclaving ing for 20 minutes at 7 lbs. pressure; temp. not given.
Lembcke[20]				Nipples washed, autoclaved for 20 minutes, placed by hand on formula-filled bottles, covered with cellophane cap. Bottles immersed to shoulder in water from 64.4° to 71.1°C. for 30 minutes. Uniformly low counts obtained from all nipples examined and in half instances no organisms were detected.

efficacy and safety of pressure cookers. It should be pointed out that very few of the studies presented gave bacteriologic evidence to support opinions.

Survey of Pediatricians, Public Health Workers, Nutritionists and Commercial Formula Companies

Opinions were then secured from 33 pediatricians all in charge of large services, one public health worker who has carried out investigations on this problem, as well

as three commercial milk companies and two nutritionists. These were obtained by the questionnaire method and the results have been tabulated as follows:

A. After the Formula Has Been Poured and the Bottle Nippled and Nippled-Capped, Is Terminal Sterilization of the Final Product Necessary?

Opinion	*Number*
Necessary	25
Not Necessary	6
No Opinion	8
Total	39

B. What are the Relative Advantages or Disadvantages of the Following Types of Terminal Handling of the Final Formula Product Which Has Been Poured and the Bottle Nippled and Nippled-Capped?

(1) Terminal sterilization at 121.0°C. for approximately 10 to 15 minutes using steam under pressure in an autoclave.

Opinion	*Number*
No opinion or comment	20
Best method	10
Effective, but not best method	6
Unnecessary	3
Total	39

(2) Terminal sterilization at 76.7° to 82.2°C. for approximately 20 to 30 minutes, using steam not under pressure in an autoclave.

Opinion	*Number*
No opinion or comment	25
Best method	6
Not adequate	4
Possibly effective, but not best method	1
Unnecessary	3
Total	39

(3) Terminal sterilization at 65.5° to 68.3°C. for 30 minutes.

Opinion	*Number*
No opinion or comment	25
Not adequate	8
Unnecessary	3
Adequate	2
Possibly effective, but not best method	1
Total	39

(4) Terminal sterilization by steam in a pressure cooker. (This method is used in hospitals with very small services.)

Opinion	*Number*
No opinion or comment	27
Would probably be adequate	7
Unnecessary	3
Not practical for large numbers	2
Total	39

(5) Other opinions Given

a) 100°C. for 20 minutes	1
b) 110°C. for 10 minutes	1
c) 82.2° to 93.3°C.	1
d) 110°C. for 10 minutes or 98.9° to 100°C. for 30 minutes	1

C. Of the above four methods under B, which do you consider to be the best method?

Opinion	*Number*
Method 1	16
Method 2	6
Method 3	1
Method 4	0
Other method best	4
All unnecessary	3
No opinion	9
Total	39

D. Do any chemical changes take place in the formula by any of the above methods which would have a deleterious effect on the baby? If so, what are the deleterious effects?

All workers expressing an opinion agreed that there was no deleterious effect on the baby. Many felt that chemical changes such as carmelization of sugar, destruction of thiamin and ascorbic acid, did take place.

E. Is it necessary in your opinion to make sure that all spore bearing organisms are killed in the final formula product fed to infants in hospital nurseries?

Opinion	*Number*
Unnecessary	16
Necessary	10
No opinion or comment	13
Total	39

It is evident from the answers received that the replies were contradictory in some instances. This apparent contradiction may have been caused by the way in which the

questions were put. At any rate, the replies would seem to indicate that thought on the problem has not been fully crystallized.

It is seen that the majority of workers felt that some form of terminal sterilization is necessary. There was some division of opinion as to the duration of terminal sterilization and the temperature required. The majority considered the safest methods to be 121°C. for approximatedy 10 to 15 minutes, or 76.7° to 82.2°C. for approximately 20 to 30 minutes. A temperature of 65.5° to 68.3°C. for 30 minutes was not considered effective. Most of those answering the questionnaires had no experience with the pressure cooker; a few felt that it might be adequate. There was further division of opinion as to the necessity of killing spore bearing organisms. All stated that terminal sterilization of the formula should have no deleterious effect on the baby and many mentioned that caramelization and destruction of vitamins B and C would take place. Nearly all individuals stated that their opinions were based on clinical grounds and not on bacteriologic data.

Summary

This report comprises a preliminary discussion of certain conditions under which formulas are prepared for newborn infants in lying-in hospitals. The general picture is one of lack of proper supervision of formula room procedures and of the unskilled personnel usually assigned to the important process of formula preparation. The conditions disclosed by this study are not peculiar to New York City alone, but merely reflect the pressing nature of the problem throughout the country.[21]

Until recently the study of formula preparation was a neglected field of investigation. A review of the literature emphasizes the lack of attention that has been paid to the problem in the past. Investigators now state unanimously that the entire procedure of formula preparation in hospitals requires revision. But the methods by which this change should be achieved are still open to study. The general opinion is that some means of terminal steam sterilization is necessary. But opinion is, however, divided as to the type of steam sterilization that is desirable, the optimal temperature that should be employed, and the time of application required. Opinions are not always substantiated by adequate bacteriologic data.

Asking those with practical experience to answer certain questions on terminal processing of formula led to no consistent conclusion. Opinions were based mainly on clinical experience and judgment. There was general agreement that subjecting formulas to high temperatures would destroy such vitamins as thiamin and ascorbic acid, and would cause appreciable caramelization of the formulas. It was thought that such changes would not have deleterious effect on the baby. Vitamin replacement therapy could be readily introduced.

It is the responsibility of hospital administrators, pediatricians, obstetricians, nurses, dieticians, and public health workers to devise safe and practical methods for preparing infant formulas and to plan the layout of the formula room. The methods recommended should be based on sound scientific data and be sufficiently simple to be carried out effectively by any person assigned to formula room duty.

Acknowledgement

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Spanish Abstract

Formula de Control en los Cuartos de Recien Nacidos en los Hospitales

Un estudio preliminar sobre la supervision y ciertas technicas de preparacion

La revision de 113 hospitales con servicio de maternidad para recien nacido ha sido hecha por miembros del departamento de Salubridad de New York. La observacion de este estudio muestra la falta de supervision en la preparacion de formulas, el uso frecuente de personas insuficientemente entrenado, y el uso limitado de algunos tipos de esterelizacion terminal. Estas deficiencias fueron mas efidentes en aquellos hospitales de pequeñas maternidades y limitados servicios de recien nacido.

Una revision de la literatura revela pocas referencias acerca de la esterilizacion terminal de las formulas. Considerable variacion en las opiniones se observa en lo que se refiere a temperatura requerida y al tiempo de aplicacion de las necesarias medidas de seguridad en las formulas. Ademas, existen diferentes opiniones con respecto al uso y valor comparativo de los metodos de esterelizacion a presion o sin presiones en la esterelizacion al vapor. Pocos o ningunos controles bacteriologicos respaldan estas opiniones. Un survey a traves de un cuestionario hecho entre 33 pediatras, un trabajador sanitario, tres compañias comerciales de leche y dos nutricionistas mostraron escenialmente la misma variacion.

La necesidad de mayores estudios controlados sobre este campo es sostenida en este trabajo.

125 Worth Street

MULTIPLE CYSTIC TUBERCULOSIS OF THE BONES

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MULTIPLE cystic tuberculous cranial lesions are uncommon. Meng and Wu[1] have reported 40 cases involving the skull, and Gibson[2] has described 32 cases involving multiple lesions over the skeletal system. These two reports point out that in countries where tuberculosis is prevalent, multiple tuberculous lesions of other bones are common.

Jungling[3] called attention to multiple cystic lesions in the bones in nine cases and chose to refer to the condition as osteitis tuberculosa multiplex cystica. The lesions he described were in the small bones of the hands and feet almost entirely, and occurred in adults. A large majority of the cases mentioned were not confirmed by recovery of the tubercle bacillus from the lesions.

In recent years Lyford,[4] Hsieh, et al,[5] Stalmann,[6] Kelly and Sailer,[7] Law and Perham,[8] Martin,[9] Fox,[10] Frost,[11] and Martin and Fogel,[12] have all reported cases of multiple tuberculous bone lesions. Most of these cases have sufficient information to confirm the diagnosis. However, since proven cases of multiple cystic tuberculosis are uncommon in pediatric literature, this being the fourteenth case reported, it seem worth while to record it.

History: No. 222,524, T.B.E., a 13 months old white male child, was admitted with a complaint of subcutaneous swellings and fever for eight months' duration.

Except for several episodes of diarrhea the child was well until he was five months of age. At that time it was noticed that he had swellings on both sides of the neck. During the eight months prior to admission swellings appeared in the axilla, in the groin, on the anterior surface of the right upper leg, on the fourth finger of the right hand, and on the right side of the head. Some of the swellings attained the size of 1.5 cm. They did not increase or decrease in size. They never suppurated nor drained. The swellings were quite tender. At times the nodes softened, only to harden again. After the eighth month of life the child neither gained nor lost weight though he ate fairly well. He ran an intermittent fever, and, for one month prior to admission here, he ran a daily fever as high as 38.8°C.

The child had been treated elsewhere with penicillin and X-ray therapy. A biopsy specimen taken from a node on the right side of the neck was sent to this hospital, and was reported as tuberculous adenitis.

Past history revealed no exposure to tuberculosis. The mother and father had had negative chest X-rays elsewhere. The child had always received raw cow's milk.

Physical Examination: On admission the patient was fretful and irritable. The temperature was 38.8°C. The anterior and posterior chain of cervical lymph nodes, the axillary, inguinal and supraclavicular nodes were moderately to markedly enlarged. In some areas, they were discrete and in others they were matted. There was a small nodular enlargement about 1 cm. in diameter over the right temple and a large swelling on the right anterior tibia. Both enlargements appeared to involve the bone. The proximal interphalangeal joint of the right ring finger was enlarged. The liver and spleen were palpable. The neck was flexible and normal reflexes were elicited.

Laboratory Studies: R.B.C. 4.4 million, Hgb. 8.5 gm., 14% band cells, 66% segmented cells, 2% large pathologic lymphocytes, 12% small lymphocytes, 4% transitional monocytes, and 2% eosinophils. There was moderate anisocytosis, many microcytic and an occasional macrocytic cell. The cells were

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FIG. 1

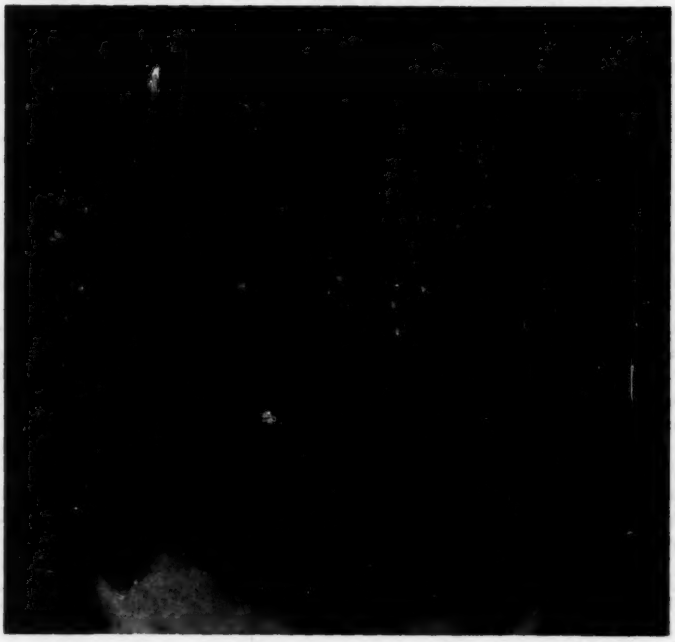

FIG. 2

FIG. 1 and 2. Skull plates showing cystic areas.

slightly oval and elongated as well as racquet shaped. There was very slight polychromatophylia. Routine tuberculin skin tests 1:1000 and 1:3000 were negative. Both human and bovine tuberculin material were used. The Schick and Wassermann tests were negative. A sternal marrow biopsy was reported as relatively acellular, with small lymphocytes predominating. There was a hypoplasia of the marrow. No foam cells were seen.

A specimen by biopsy taken from a node in the right axilla contained scattered minute abscesses, some of which contained giant cells. The lymph node was infiltrated with polynuclear leucocytes and scattered throughout there was hemorrhage and necrosis. Tubercle bacilli were demonstrated. An aspiration biopsy of the left femur showed bone marrow in which there was a chronic inflammatory

FIG. 3. Pelvic plates showing widespread cystic areas in pelvis and femurs.

and granulomatous reaction. There were areas of localized necrosis surrounded by a proliferation of epitheloid cells. These revealed tubercle bacilli.

Roentgenologic examination of the chest was negative. The ribs showed a marked destructive change particularly on the right. The humerus on either side showed the same type of change. The same type of destructive change was noted in the proximal phalanx of the right ring finger. The pelvic film showed the same type of changes in the pelvis and in the femora. The cortex was broken through in several areas.

Films of the skull showed round discrete areas measuring from 2 mm. up to 2 cm. scattered throughout the skull. There was a complete destruction of both the inner and outer tables with sharp borders. These lesions varied in size and shape. The lesions in the skull were similar to those seen in the other bones.

Hospital Course: The patient remained in this hospital 12 days. On admission he weighed 7.1 kg. He ate and took fluids very poorly. He was very irritable. Temperature varied from 37° to 38.8° and 40°C. On one occasion it was 41°. On discharge, he weighed 6.2 kg.

Discussion

Jungling[3] described tuberculous bone lesions which were almost always confined to the bones of the hands and feet, while Kienböck[13] described lesions involving only the long bones. Other reports mention cases involving the flat, small and large bones. It is generally agreed that these lesions occur secondarily to tuberculosis elsewhere and the infection is spread by the blood stream. Therefore, the nomenclature is not important as the disease process is the same as was stated by Law and Perham.[8] This patient had cystic tuberculous lesions in the flat and long bones as well as in the bones of the hands and feet. This combination would seem quite rare. Frost[11] and Martin and Fogel[12] have each reported a similar case but without recovery of the tubercle bacillus from the actual lesions.

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Spanish Abstract

Tuberculosis Quistica de los Huesos

La existencia de lesiones de quistes multiples oseos es considerada infrecuente. Este caso es el catorce reportado en la literatura pediatrica.

Se trata de un niño de trece meses ingresado en el Hospital Universitario de Virginia ofreciendo una hinchazon subcutanea con dolor y fiebre de ocho meses de duracion. La primera hinchazon fue notada a los cinco meses de edad y entonces aparecio en la axila, en la pierna derecha en un lado de la cabeza y en los dedos. Nunca fue drenada o separada. Ha sido visto en todas partes y una biopsia de glandulas del cuello fue reportada de positiva de tuberculosis.

El examen clinico revelo un niño enfermo con las lesiones descriptas arriba. El higado y el bazo estaban ligeramente aumentados. Los examenes de laboratorio fueron todos negativos e inclusive la prueba de tuberculina realizada con tuberculina procedente de bacilos humanos y bovinos fue negativa, pero la biopsia del material tomado de las lesiones oseas ofrecieron el cuadro tipico de tuberculosis y ademas en este material se comprobo la existencia del bacilo de tuberculosis.

El examen por los Rayos X mostro muchas areas quisticas en los huesos de todo el cuerpo.

University of Virginia Hospital

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Symposium

ON PEDIATRIC SURGERY

HERBERT E. COE, M.D., *Chairman, Seattle, Wash.*

Chairman Coe, **Introduction:**

Many of us remember the period when pediatrics consisted largely of a complicated process of infant feeding and the treatment of colds and bowel disorders. Our ideas have undergone a constant evolution until now the concept of pediatrics is the complete care of individuals during that developmental period known as infancy and childhood—a period characterized by rapid physical, mental and environmental change. The conditions affecting this period are numerous and diverse, and this section of the program has been set aside for the presentation of several of those conditions which have a surgical connotation. Children's surgery, which has been consistently and soundly developed by Ladd of Boston, has been given definite recognition by the establishment by Harvard of the Ladd chair of children's Surgery, which to the best of my knowledge is the first such professorship in this hemisphere, if not in the world.

The surgery of this period of life is in the highest degree physiologic surgery as distinguished from excision surgery, the surgery of evolution instead of involution, and it requires particularly close attention to the caloric, fluid, and electrolytic demands of growth—all of which concepts are fundamental in the care of children.

The idea is commonly current that children's surgery is synonymous with the so-called "surgical abdomen"—as typified by a panel discussion in the tentative program for the approaching series of sectional meetings of the American College of Surgeons entitled "Pediatric Surgery (or abdominal surgery in children)." This concept completely disregards the neo-natal surgical emergencies, the surgery of the extra abdominal congenital defects, neuro-surgery, the plastic surgery of accident and scars so characteristic of this irresponsible period of life and the high proportion of children in the surgical practice of the orthopedist and the otolaryngologist.

To the best of my knowledge there is no national organization in which the various aspects of children's surgery can be as well correlated as in this Academy and it is the opportunity and obligation of pediatricians personally and of our Academy officially to promote better surgical care for children by stimulating advances in this branch of surgery and by providing an organization for the discussion and analysis of its problems and a medium for the reporting of research and the dissemination of information.

From the Annual Meeting of the Academy, Dallas, Tex., December 8-11, 1948.

The participants in the symposium have for many years confined their professional activities either entirely or in large part to the surgical care of children and their recognized ability qualifies them to speak with authority.

Dr. Willis J. Potts, Chicago, Ill., **Inguinal Hernia in Infants:**

Our rather unusual experience with inguinal hernia in infants at the Children's Memorial Hospital during the past year prompts the writing of this paper. Because the figures are for only one year they are not presented for percentage quotation. During this time 32 infants less than 18 months of age were operated upon for inguinal hernia. Seventeen had simple uncomplicated hernias; five had hernias with associated hydroceles. In ten patients the hernia was incarcerated and could not be reduced before operation. In five of this group the bowel showed various stages of congestion which cleared when the construction was released. One baby, a premature infant, weighing only 1600

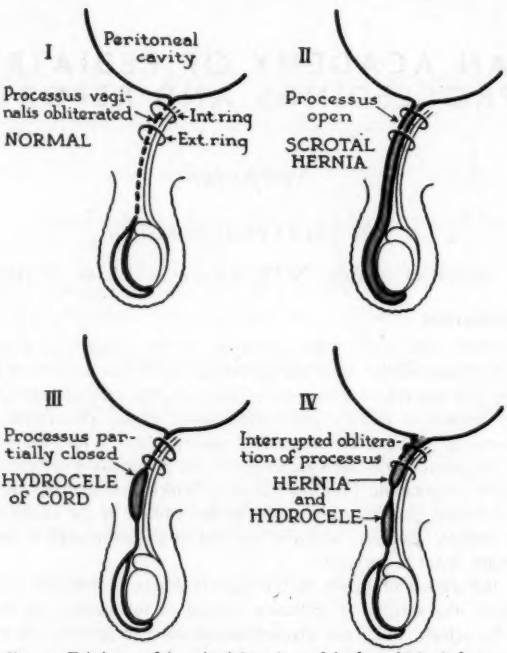

FIG. 1. Etiology of inguinal hernia and hydrocele in infants.

gm. and evidently had an incarcerated hernia for some time before admission to the hospital. At operation strangulation of the bowel was apparent. The child's condition was very poor. Because the bowel was blue black but seemingly intact it was decided that the risk of simply replacing the bowel in the abdomen was less than that of resection. The decision was wrong. The baby died in two days and at postmortem examination peritonitis as a result of perforated small intestine was found. Furthermore, in two of the children with incarcerated hernias the testicle was black due to strangulation. Complete atrophy of the testicle has followed in both.

This unusually high percentage of incarcerations and associated complications, although not likely to be repeated in any future year, indicates the importance of intelligent handling of the simple but oft recurring problem of hernia in infancy.

ETIOLOGY

The etiology of inguinal hernia in infants is extremely simple. All are indirect and all are congenital due basically to one factor alone—failure of the processus vaginalis to obliterate itself normally. Persistent cough, constipation, excessive crying and phimosis are merely contributing factors which tend to break open a processus improperly closed. Variation in degree of obliteration of the

processus vaginalis accounts for various degrees of hernia and for the formation of hydroceles (Fig. 1). If the entire processus remains open the hernial sac obviously extends all the way to the testicle. Obliteration of the distal portion usually results in a small hernia with a short sac, where as obliteration of the proximal portion only may result in the formation of a hydrocele. Segmental obliteration of the processus leads to the development of coexisting hernia and hydrocele. Nothing could be simpler.

Diagnosis

The diagnosis of inguinal hernia in an infant is easy when the baby is brought in with a bulge in the inguinal region which can be reduced with a gurgle discernible to the palpating finger. It is less simple when the mother says that she has seen a lump in the groin once. Stimulating the baby to cry will not bring out the hernia. Palpation of the internal ring with a finger is unsatisfactory and inconclusive. Palpation of the inguinal canal, that is, rolling the tip of the finger transversely across the structures of the cord, will if a hernia is present, impart a sensation of rubbing silk surfaces together. This maneuver is of value but requires considerable experience before one feels confidence in it alone as diagnostic. At times one has to admit that a diagnosis is impossible and further observation will be necessary.

A similar problem in diagnosis is posed when a definite hernia is present on one side and the mother thinks that there may be another on the opposite side. If surgery on one side is decided upon it is very wise, if for self protection only, to examine the other side and make a note with the date that at this examination the hernia is unilateral. Not infrequently, if by pure coincidence a hernia appears on the opposite side after operation, the mother blames the physician or the surgeon for overlooking the second hernia.

To distinguish a hydrocele from a hernia is theoretically simple but sometimes impossible. I have been wrong oftener than I am happy to admit. The small, oblong, unchanging in size, not tender, fluctuant, light-transmitting mass in the cord, or the characteristic collection of fluid around the testicle is instantly recognizable as a hydrocele. However, when the mother says that the mass in the groin is smaller in the morning and enlarges slightly during the day after the infant stands in its crib or cries, one is suspicious that the mass, although irreducible, is probably a hernia with a small opening. Both hydrocele and hernia may be present. Since it is not our policy to operate on hydroceles in infants it is important to distinguish them from hernias. When a differential diagnosis is impossible and subjective symptoms are absent further observation is in order.

A frantic mother brings her baby in with a mass in the groin which she says appeared suddenly. The baby is screaming—whether because of pain in the groin or on general principles is not readily ascertainable. The mother is convinced that the baby has an incarcerated hernia about which she has heard reports and the examiner is not sure. The mass is irreducible but transmits light readily. Fluid and air in the intestine will transmit light. Nothing is more disconcerting than to put a needle into such a mass for diagnosis and to withdraw intestinal contents. The impulse to solve the problem quickly with a diagnostic needle should be curbed. Usually a little time spent in soothing the child with a bottle and the mother with an air of confidence is all that is necessary, plus a second examination, to differentiate a suddenly appearing hydrocele from an incarcerated hernia.

Treatment

Authentic medical literature abounds in a variety of advice concerning the treatment of inguinal hernia in infants. Some writers, especially those who wrote at the turn of the century, say that most hernias in infants will disappear with the use of a proper truss. Others claim that very few hernias will be cured permanently by the use of a truss. To the latter claim I now subscribe unqualifiedly. A truss will support some hernias fairly well but that is all. I do not believe any truss on the market will cure more than a very occasional hernia and I am inclined to believe that the "cured" hernia is potentially still there and is apt to appear with any sudden strain. Many times a child has been brought in with a fancy high-priced truss in place—the hernia held firmly in the scrotum. The mere presence of a truss gives the mother a false sense of reassurance that nothing can happen. Infants are brought in with all sorts of trusses—the pads resting anywhere between the symphysis and the umbilicus. It stands to reason that a truss can't cure most hernias because it is next to impossible to keep a hernia reduced for weeks, 24 hours each day. If the infant cries or strains while the truss is removed for cleaning or during the bath the hernia comes out and all that may have been gained in sealing the surfaces of the processus vaginalis together is lost in an instant. The faith that is placed in a yarn truss is amazing. A twist of yarn in the inguinal region holding

a hernia reduced in a vigorous infant who objects strenuously to the mode of life imposed upon him—that is faith, not reality.

Approximately ten years ago I worked on and developed a simple, homemade truss for infants. It was described in J.A.M.A. 117:1440, 1941. The truss has proven fairly effective in keeping a hernia reduced and is still used when indicated but even it fails to "cure" hernias.

In this same article I made a few statements which I wish to retract. "Surgical repair of inguinal hernia in children below two years of age is rarely indicated except in emergencies. . . . The surgeon hesitates to operate because some hernias, specially in very young infants, disappear spontaneously."

The treatment of inguinal hernia in infants, *otherwise normal,* is surgical regardless of age. The infant who is in poor condition because of congenital variations from normal or because of disease should be treated with a truss, if treatment is necessary, until it is in condition to undergo surgery.

Manual reduction of an incarcerated hernia is preferable to surgical. A hernial sac which is friable and edematous because of constriction is difficult to dissect out and dispose of properly. It often tears. It is more satisfactory to operate in a few days after the edema has disappeared. An

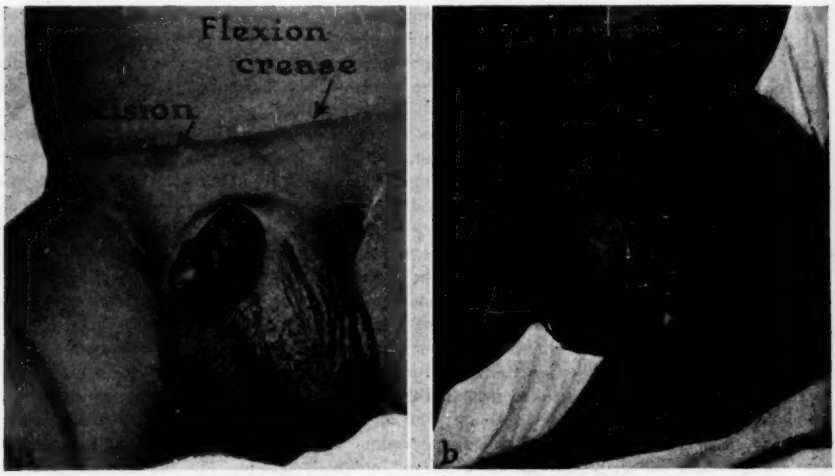

FIG. 2. A. Incision in suprapubic skin crease. B. Appearance of incision upon completion of operation.

incarcerated hernia can often be reduced by continuous but very gentle pressure while the infant is concentrating on a nipple well reinforced with sugar. If simple pressure fails and there seems to be no urgency for reduction the baby is given a sedative such as nembutal and adhesive tape for traction is applied to the legs. Sufficient weight is attached to raise the baby while only its shoulders and head touch the bed. After an hour or two if this elevation plus some more gentle pressure is ineffective in accomplishing a reduction of the hernia, surgery is indicated at once.

Surgical repair of an inguinal hernia is a simple but delicate operation. The technic of repair is as follows: under open mask ether anesthesia, a small transverse incision is made in the suprapubic crease through the skin over the region of the internal ring (Fig. 2). The incision is made in the skin crease rather than along conventional lines because it seals itself more rapidly and is therefore less apt to be contaminated by urine or feces. Such an incision, made along the lines of cleavage, heals more readily and with less tendency towards keloid formation. That the ultimate scar is scarcely visible is of no practical importance but is a source of pleasure to the mother.

The external oblique is exposed and split (Fig. 3-1). The external ring is not cut unless the hernia is very large and the ring has been stretched. In most instances it is possible to isolate the sac without opening the ring. One of the main causes of post-operative swelling of the testicle is too snug closure of the external ring.

The fascias and cremasteric muscle fibres over the cord are easily slit longitudinally. The sac comes into view and is drawn up out of its bed disturbing the cord as little as possible. The sac is opened tnd the interior carefully inspected. Usually the bowel has fallen back into the abdomen. Omentum is not found in the sac in infants. Great care is necessary in dissecting the sac from the

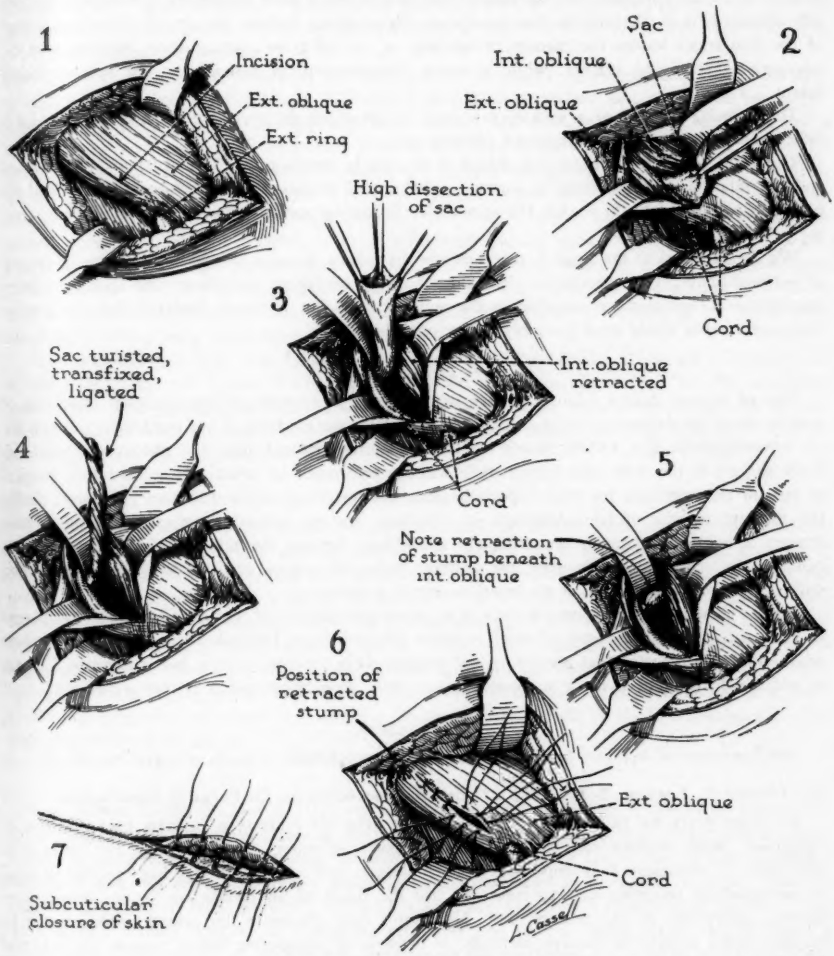

FIG. 3. Technic of herniotomy for infants.

structures of the cord. A tear into the neck of the sac makes repair difficult and unsatisfactory. The vas, little larger than a silk thread, is attached intimately to the sac and must be peeled off carefully.

The most important step in the operation, in fact, *the sole object of the operation is to ligate the sac high* (Fig. 3-5). The internal oblique is retracted outward and the interior of the sac again inspected. The sac is then twisted until the properitoneal fat begins to rotate about the twisted sac. Appearance of this properitoneal fat leaves no doubt that the entire processus is obliterated. The sac is transfixed with silk and doubly ligated. When the sac distal to the ligature is cut and the retractor beneath the internal oblique muscle removed, the stump of the sac will be seen to snap up beneath the internal oblique muscle.

The structures of the cord are allowed to fall back into their normal position. No repair of the hernial floor is done. The object of the operation—to remove the processus vaginalis which nature failed to obliterate—has been accomplished. Why do more?

With a few silk sutures the opening in the external oblique is repaired. Two or three deep sutures in the fat obliterate the dead space. The skin is closed with interrupted subcuticular No. 6-0 silk sutures (Fig. 3-7). Subcuticular sutures are advantageous because the almost immediate sealing of the skin edges lessens the chances of infection in case of gross contamination. Avoidance of the necessity of removing stitches, while a minor consideration, is desirable in the normal wiggly infant.

The dressing consists of a very narrow strip of gauze which covers the hairline incision and is held in place with a strip of waterproof adhesive tape.

The child is returned to its crib where it is entirely unrestrained. The usual diaper is put on and the infant is given its regular formula as soon as it wishes. If the mother wishes to hold the baby she is allowed to do so. On the second day following operation the patient is dismissed from the hospital.

We are indebted to the English surgeons who have been pioneers in advising the type of surgery as outlined above. They operate on these infants in the outpatient department and send them home immediately. This seems reasonable in the simpler cases but it seems doubtful that the average American mother would react favorably to that procedure.

Discussion

Fear of surgery during infancy, or lack of confidence in operating upon miniature structures, or anxiety about the dangers of wound infection, or perhaps the teaching of our forefathers prompts the oft repeated advice that a child should not have its hernia repaired until it is two to four years old. Since surgery is the only cure (about 99% without recurrence in infants) it seems rather illogical to put off the operation for years especially since the percentage of incarceration is greatest during the first six months of life. Although no operation and no general anesthesia is without some danger, a herniotomy carries an extremely small risk. Against the minimal risk of operation is balanced the anxiety of the mother, the constant bother of a truss, and the danger of incarceration with consequent strangulation of the bowel or loss of a testicle.

Besides these negative advantages there is an occasional unexpected reward following a herniotomy. In the small group of patients referred to above operated upon last year there were three mothers who voluntarily reported that hernitomy had relieved their children of colic and irritability. I hasten to add that herniotomy is not a suggested cure of colic. As a by-product it is very acceptable.

Conclusion

The treatment of inguinal hernia in otherwise normal infants is surgical regardless of age.

*Dr. Thomas H. Lanman, Boston, Mass.,** **Urinary Incontinence; Its Surgical Significance:**

For many years the pediatrician has been on the alert for evidence of urinary tract infection in childhood. With modern methods of treating urinary infection, the results are far better than they were 20 years ago. It is important to re-emphasize, however, that a very high percent of cases of persistent or recurring urinary infections are the result of an obstructive lesion, usually congenital, somewhere in the urinary tract. No matter how efficiently the urinary infection can be brought under control by modern methods, if there is an obstructive lesion present, the infection will inevitably recur. This was well shown by autopsy figures some years ago. A high percent (about 50%) of young children dying of pyelonephritis showed some mechanical obstructive lesion which might have been amenable to surgery, had its presence been recognized in time.

Of late years, we have been equally impressed with the great significance of urinary incontinence in infants and children. I shall discuss briefly some of the conditions that cause urinary incontinence, and will stress the importance of the early recognition of these causes. By far, the most important causes are obstructive lesions that are present at birth. These are particularly dangerous in that during the first few months of life the infant is not supposed to have urinary control, and unless there is careful observation by mother or physician, certain symptoms may pass as being due to

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the normal, but untrained infant. A second group of causes includes those whose symptoms appear at a later age and it is of the utmost importance that should a previously trained young child develop symptoms of incontinence, the cause be most carefully searched for.

The most insidious, the most dangerous and the most frequently overlooked cause of incontinence during infancy is some obstructive lesion at the bladder outlet. It is more commonly found in boys and the most frequent lesions are congenital obstructive valves in the posterior urethra. The following is a typical, though extreme, case.

A 2½ year old boy was constantly dribbling urine. The mother stated she had never been able to train him like her other children. Two days before admission there had been some hematuria. Examination showed an ill-nourished child with marked distention of the lower abdomen and a mass palpable 1 cm. above the umbilicus. There was a mass in the right kidney region. The urine dribbled from the urethra every 10-15 minutes. On catheterization, which was easily accomplished, the mass in the midline disappeared. Cystogram showed typical findings of trabeculation of the bladder, and dilatation of the prostatic urethra. The child's breath had a uremic odor and his general appearance resembled closely that of an elderly patient with long-standing prostatic obstruction. The non-protein nitrogen was 280 mg./100 cc. blood. Function tests showed extensive kidney damage. The findings suggested by the examination were confirmed at operation. The valves were sectioned and although the child improved somewhat, the damage to his kidneys was irreversible, and death followed some weeks later.

The "incontinence" here was dribbling of the overdistended bladder. This case illustrates one of the most dangerous types of congenital malformation we encounter. It is seldom recognized before irreversible damage has been done to the kidney. Such an infant, even though he has not reached the age when voluntary bladder control is usually obtained, has a constant "dribbling incontinence" from his overdistended bladder.

Ureterocele

This obstructive lesion usually results in repeated attacks of urinary infection, but the ureterocele may become of sufficient size to actually obstruct the bladder outlet and, by so doing, give rise to the additional symptom of dribbling from the overdistended bladder. Here again, it is of the utmost importance that the obstructive lesion be recognized early, as it is readily remedied by surgery with complete relief of symptoms unless, as a result of long-standing obstruction, there has been irreversible damage to the kidneys. In this group of cases, it is particularly significant that some have come for treatment with the usual story of recurring attacks of pyuria and also, in the more advanced cases, have given the history that the child was normally trained at the usual time, but subsequently began to develop symptoms of urinary incontinence which were the result of the overdistended bladder with obstruction at its outlet.

Tumor

New growth of the bladder is relatively rare in this age group, but it carries an exceedingly grave prognosis. In our small series of bladder tumors almost all have been rhabdomyosarcomata. Urinary incontinence has been striking. In those children below the age of two, it was overlooked because it was not recognized as the dribbling of an obstructed bladder and, in some cases, the symptom appeared in later years of childhood when there had been a considerable period of time with normal bladder control. A cystogram, especially one in the lateral view, usually shows a characteristic filling defect in the bladder; an irregular one in tumor, and a rather smooth, rounded shadow in ureterocele.

Some of the rarer conditions are illustrated by the following:

Foreign Body

An eight year old girl had previous normal development up to the age of four, and at that time had normal bladder control. For the next two years she had symptoms of incontinence, but it was two years later that an X-ray was taken and showed that there was a foreign body in the bladder. A hair pin had apparently been inserted into the bladder about the age of 4 and had eroded through to the anterior vaginal wall. The main thing here is to again call attention to the fact that in a child who has developed normal control and then becomes incontinent, a most careful study is warranted.

Another case of incontinence was caused by a stone encysted in the remnants of the urachus.

This was a boy of nine who, up until the age of seven, had apparently normal urinary control. He had no symptoms of urinary infection and for months was treated as a problem child. The calcified lesion in the urachal cyst hung down within the bladder itself and, presumably, caused the symptoms which, properly speaking, were more those of urgency with incontinence, rather than true incontinence. A plain X-ray film gave an immediate clue which resulted in further investigation and had this simple step been taken some months sooner, a great deal of unnecessary delay and annoyance to the family might have been prevented. Removal of the stone resulted in complete cure.

Ectopic Ureter

There are an increasing number of cases of ectopic ureter coming to our attention. These are more frequent in the female and the ectopic ureter, which is usually one of a double ureter on that side, empties into the urethra distal to the bladder sphincter. It is obvious that the urine which this ureter excretes from that part of the kidney which it drains, cannot be controlled because this ureter empties distal to the bladder outlet. We made the mistake of treating a patient of this sort for a number of months as a "problem child," and in the cases we have seen since this has been the common history.

Fortunately, the last two types of anomalies mentioned do not, as a rule, lead to any serious impairment or infection of the kidneys and are, therefore, not as urgent as some of the other types mentioned. It is, however, very embarrassing to attempt to treat over a long period of time by psychiatric methods a child who has a lesion such as an ectopic ureter which by its very nature precludes any voluntary control over the excreted urine. The intravenous pyelogram is simple to obtain and will usually give reliable information in establishing the diagnosis of ectopic ureter.

I shall speak of exstrophy of the bladder, which is an obvious anomaly and with obvious reasons for incontinence, only to say that with our present technic we can offer good assurance, not only of urinary control, but of minimal retrograde infection of the kidneys when the ureters have been transplanted into the sigmoid. In over 50 cases, we have had no deaths following transplantation. Intravenous pyelograms, as long as 15-16 years after the transplantation, show gratifyingly little evidence of retrograde infection. Not in all cases, of course, but in the great majority. We believe this operation is best done between the ages of 2 and 5 years. The child is then old enough to cooperate more intelligently in acquiring control of the rectum and he is not yet of school age. In our series, there is little, if any, evidence to make us believe that postponing the operation for two to three years after birth carries any appreciable danger of retrograde kidney infection, as a result of the exposed ureteral openings in the exstrophied bladder. Certainly, it is reasonable to assume that transplanting the ureters into the sigmoid moves them into an area fully as contaminated as was their location before transplantation.

As pediatricians, it is well to remember that the problem of the exstrophied bladder in the male is very much complicated by the associated epispadias, repair of which, even at best, leaves much to be desired from the cosmetic and functional point of view. The psychologic effect on the male of urinating in the sitting down position plus the external appearance of the genitals is a very real problem. In the female this does not present any difficulty. In both sexes, assurance of good urinary control can be given, but in the male this is by no means the entire solution to the problem.

There is another very distressing type of urinary incontinence, usually associated with rectal incontinence. In this age group it is largely the result of spina bifida with meningomyelocele. These patients present a most distressing situation, but in a few cases we have had moderate success by transplanting the ureters to a blind lower sigmoid loop, the distal end of which is close to the rectum and is permanently closed; the proximal end being brought out through the abdominal wall on one side of the abdomen and this opening emptied at regular intervals by the use of a catheter. The open end of the sigmoid, just above this blind loop used as a bladder, is also brought out through the abdominal wall on the other side and the feces are taken care of by a colostomy bag. These methods alleviate to a considerable degree, the very distressing situation, but it is too soon to estimate as yet, how great a degree of retrograde infection may take place.

This brings me to a discussion of the question of spina bifida occulta. As is well known, evidence of faulty development in the lumbo-sacral spine is an extremely common incidental finding when X-ray films that include the lower spine are taken. Roughly, about one-third of all the cases taken at our clinic show some developmental anomaly, usually incomplete fusion of the spinous process of

one or more vertebrae. In 1,000 cases of spina bifida at this clinic, 91 or, roughly 10% were classified as spina bifida occulta which demanded further study because of symptoms, usually bladder symptoms. Of these 91 cases about 25% gave enough on history or physical examination to warrant the assumption that this bony defect was associated with some nerve disturbance which resulted in the symptoms of urinary incontinence. Exploration of the spinal cord was done. As Dr. Ingraham will show, the exploration of these cases showed in a very large percent of cases that there was a definite lesion, usually some tumor formation, the removal of which offered relief of the bladder symptoms. Associated with this type of case are those of definite intraspinal tumors which has again been well covered by Dr. Ingraham. It is mentioned here and emphasized that not only must careful urologic examination be made on children presenting the symptoms of urinary incontinence, but also a very careful neurologic examination, in appropriate cases.

SUMMARY

There are a surprisingly large number of anatomic and developmental defects that result in urinary incontinence in infancy and childhood. While most cases of "enuresis" are merely the result of inadequate or improper training, the doubtful case should receive careful neurologic and urologic studies before psychiatric therapy in its various forms is undertaken. It is particularly important to study such cases in instances where urinary control has already been established and then the symptoms of incontinence develop.

The most dangerous cases of all are those due to some defect which results in the "dribbling incontinence" of an overdistended bladder. These are particularly dangerous, in that the "incontinence" may be regarded during the first year or two of life as only the normal lack of training on the part of the child. The difference between this and pathologic lack of control is usually easily apparent. The normal child allows his bladder to become full, empties it all at once, and then will remain dry for varying periods of time. In obstruction, with overdistention of the bladder, the lack of control is constant, is small in amount and, if this possibility is considered, diagnosis of an obstructive lesion is easy. Urethral valves may be removed, but bladder tumor has a grave prognosis. Neurologic cord lesions also present a constant, though variable degree of incontinence day and night, and careful history will bring this out. Ordinary enuresis is inconstant.

300 Longwood Ave.

Dr. J. B. Campbell, Boston, Mass., (in absentia), **Spina Bifida:** (Review by Dr. Ingraham.)

Dr. Jesús Lozoya S., Mexico City, D. F., **Intestinal Perforation Complicating Typhoid Fever in Children:**

From the month of July 1943 to August 1946 there were 15,688 admissions to the Hospital del Niño, México City; 457 were definitely diagnosed as typhoid fever (typhoid and paratyphoid fevers), i.e. 2.91% of the admissions. Of these 457 cases, we had 33 cases of peritonitis (7.22%) of which 29 were perforations of the ileum (6.35%) and 4 cases were by rupture of the gall bladder (0.87%).

Besides, there were three cases of acute cholecystitis for whom we felt operation was not indicated and that were cured by medical treatment without having had a rupture of the gall bladder.

TABLE I

	Cases	Percent
Admissions July 1943, August 1946	15,688	
Typhoid Fever	457	
Percentage on admissions T.F.		2.91%
Peritonitis among the T.F.	33	7.22%
Peritonitis due to perforated intestine	29	6.35%
Peritonitis due to rupture of gall bladder	4	0.87%
Cholecistitis cured without operation in which there was no perforation	3	0.66%

TABLE II

No.	Name Reg.	Age (Years)	Days of Evol.	Days of Perforation	WBC	Aglut. Test	Culture	No. of Perforations	Enteric Hemorrage	Diarrhea	Poor Feeding	Purge Enema	Operation	Living
1	R.R.L. 5741	11	30	10	—	Eberth: 1×500	—	1	+	+	+	+	—	No
2	G.A.T. 14495	8	14	8	—	—	Peritoneal fluid: Eberth	1	+	−	+	+	Suture of perforation. Drainage.	No
3	H.P.A. 14738	7	47	3	—	—	—	2	−	−	+	+	Suture of perforation. Appendectomy. Drainage.	No
4	C.V.E. 14739	10	26	4	—	—	—	1	−	−	+	+	Suture of perforation. Drainage.	No
5	A.P.S. 14766 —	10 —	29 —	3	3360 Neut: 70 Infectious panmyeloptisis.	Eberth: — 1×200	Positive in blood.	1	+	−	+	+	Appendectomy. Suture of perforation. Drainage.	No
6	N.P.C. 14700	5	15	3	4600 Neut: 38	Eberth: 1×100	Positive in blood	1	−	+	+	+	Suture of perforation. Drainage.	
7	P.L.M. 754	11	53	11	4000 Neut: 59	Eberth: 1×200 H: 1×500 Brucelis: ×200	Negative	1	−	−	+	+		No
8	G.G.H. 22750	9	21	3	3280 Neut: 89	Eberth: H: 1×500 Para. A: 1×50 Prot. X-19 1×50	—		+	+	+	+	Not operated on.	No
9	A.G.G.	8	24	48 hours	4800 Neut: 44	Eberth: 1×500	Negative		−	+	+	+	Drainage.	No
10	C.C.R. 359	8	34	4	2960 Neut: 77	Negative	Negative	5	−	−	+	+	Resection Drainage.	No
11	M.C.F. 9801	6	18	2	2920 Neut: 80	Eberth: O: 1×100	—	1	+	−	+	+	Suture of perforation. Drainage.	No
12	L.C.C. 9399	8	30	4	3280 Neut: 89	Eberth: 1×500	—	1	+	+	+	+	Not operated on.	No
13	R.Q.S. 42054	11	31	3	4520 Neut: 80	Eberth: H: 1×100	Negative in feces	1	+	+	+	+	Suture of perforation. Drainage. Enterostomy.	No
14	F.P.R.	7	40		3320 Neut: 78	—	—	−	−	−	+	+	Not operated on.	No

14	F.P.R.	7	40		3320 Neut: 78	—	—	—	—	—	+	+	Not operated on.	No

TABLE II—(*continued*)

No	Name Reg.	Age (Years)	Days of Evol.	Days of Perforation	WBC	Aglut. Test	Culture	No. of Perforations	Enteric Hemorrage	Diarrhea	Poor Feeding	Purge Enema	Operation	Living
15	B.C.F. 35815	12	13	4	3440 Neut: 77	H: 1×200 O: 1× 50 A: 1× 50 B: 1 ×50	—		−	+	+	+	Not operated on.	No
16	R.H. 35612	12	48	15	13360 Neut: 89	O: 1×50 B: 1×50	Blood: negative		−	+	+	+	Not operated on.	No
17	G.S.C. 35349	3	12	7	4200 Neut: 62	Negative	Blood: negative	Several	−	+	+	+	Drainage.	No
18	R.T.R.	10	25	5	6280 Neut: 80	Negative	—	1	−	+	+	+	Suture of perforation. Drainage.	No
19	L.C.L. 9399	8	22	4	3200 Neut: 55	Eberth: 1×500			+	+	+	+	Not operated on.	No
20	A.C.J. 986	8	14	1	10200 Neut: 61	Eberth: 1×500		1	−	+	+	+	Resection. Appendectomy. Drainage.	Yes
21	S.L.G. 14335	9	40	1½	14080 Neut: 88	Eberth: 1×500	Pus: positive Eberth	1	−	+	+	+	Suture of perforation. Drainage.	Yes
22	G.I.T. 13217	13	15	1	25640 Neut: 47	Eberth: 1×200		Many	+	−	+	+	Resection. Drainage.	Yes
23	D.D.J. 22129	6	20	2	18000 Neut: 75	H: 1× 50 O: 1×200	Blood: negative	1	−	+	+	+	Suture. Drainage.	Yes
24	S.S.A 142	10	20	—	11120 Neut: 38	Eberth: 1×50	Blood: negative		+	−	+	+	Not operated on.	Yes
25	S.S.H. 24847	11	18	3	18500 Neut: 88	Eberth: 1×500	Blood: negative	1	−	+	+	+	Suture. Drainage.	Yes
26	L.G.D. 38919	4	7	3	11760 Neut: 94	H: 1×200 B: 1×100	Blood and feces: negative	1	−	+	+	+	Suture. Drainage.	Yes
27	V.T.G. 42111	6	21	1½	10960 Neut: 77	H: 1×200 O: 1× 50 A: 1× 50 B: 1×200	Blood: negative	1	−	−	+	−	Witzel's Enterostomy.	Yes
28	V.E.C. 42759	3	21	1	12300 Neut: 86	H: 1× 50 O: 1×500 B: 1× 50	Blood: negative	1	−	−	+	+	Witzel's Enterostomy. Drainage.	Yes
29	R.F.C. 38866	7	13	1	3680 Neut: 80	H: 1×200 O: 1×500 A: 1× 50		1	+	+	+	−	Suture Drainage: Muller: AB Bot tube resection.	Yes

TABLE III

Rupture of the Gall Bladder Due to Typhoid Fever—July 1943 to August 1946

Case	Name Reg.	Age (years)	Days of Evol.	W.B.C.	Aglut. Test.	Culture	Enteric Hemorrhage	Diarrhea	Poor Feeding	Purge Enema	Peritoneal Puncture	X-Ray Air without Pneumoperitoneum	Operation	Living
1	M.M.L. 9326	9	38	13920 Neut: 91	H: 1×500 O: 1×500	Blood: negative — Peritoneal pus: coli B— and Staph.	+	+	+	+	Pus and bile	+	Cholecystectomy — Drainage	5 days
2	H.D.E. 14130	9	33	9040 Neut: 84 Myelogram: toxic infectious reaction	Eberth: 1×500	Blood: negative — Peritoneal pus:typhic bacilli	+	−	+	+	Pus and bile	+	Cholcystectomy — Drainage	Healed
3	M.T.M. 1452	6	30	7400 Neut: 85	Eberth: 1×500	Peritoneal pus: typhic bacilli	−	−	+	+	Pus and bile	+	Drainage marzupialization	10 days
4	C.A.M. 14845	10	37	2850 Neut: 90	H: 1×100 O: 1×100	Blood: negative	−	−	+	+	Pus and bile	+	Marzupialization drainage	6 days

This represents 0.66% of the total typhoid cases admitted. Table II is a detailed account of the 29 cases of intestinal perforations of each individual patient, the age, the progress or rather the number of days prior to hospital admission with probable duration of the perforations. WBC percent of neutrophiles are mentioned in Table II, except for the monocytes, lymphocytes and eosinophiles, left out in the order to simplify the picture. The Shilling index and myelocytes are also deleted for the same reason. Suffice it to say that, in all, there was more or less marked reaction of the young form in proportion to the severity of the infection; we recorded the agglutination tests and the cultures in blood, peritoneal fluid or feces; the operations performed were: in three cases drainage of the peritoneum only, while in the others, drainage plus suturing of the perforation with chromic catgut, in 4 cases; resection of a portion of perforated terminal ileum with an ileolateral anastomosis was done; ileolateral anastomosis was performed in those cases where there were several perforations or a single one surrounded by a large zone of necrosis which made it impossible to do simple suturing. In the last cases we altered our technic using that of Witzel, because we feel that it is very efficacious in decompressing the intestines which are abnormally distended.

The table indicates the number of perforations found in the loops that could be seen in the right iliac fossa. In these cases the adhesions were not destroyed; the pus and fecal matter were aspirated, compressing afterwards the abdominal wall to make sure that the intestinal contents were not extruding through other openings except those under consideration. These perforations were always found in Peyer's patches. At this point we must stress a fact not indicated in the table for lack of space but which is very important: in approximately 60-70% of cases we found ascaris lumbricoides inside the intestines, or in the peritoneal cavity. The vomitus or feces of the patients, postoperatively, often showed the parasites also; we feel that ascaris lumbricoides may be a determining cause of perforations in acute typhoid with extensive ulcerations of Peyer's patches. Intestinal hemorrhages with or without diarrhea are also indicated in the table and show the frequency of both situations. All the patients were suffering from malnutrition before hospitalization. The use of purgatives and enemas, unfortunately too frequently given amongst our people, contributed greatly to the frequence of intestinal hemorrhages and perforations. Finally, we see in the table the incidence of survival and the rest is self-explanatory.

Table III is like the previous one, except that it refers to gall bladder perforations and it lacks the period of onset of perforation because a history was not always obtainable, but in most instances the duration was a week or more. WBC agglutination tests are indicated as in Tables II-A and II-B. In three of these cases, a culture of the peritoneal pus was done and we found E. typhosa in two and staphylococcus with Esch. coli in the other; in the fourth one no culture was done. Bile was found in every case in the peritoneal pus. We did two cholecystectomies and two marsupializations, bringing the gall bladder out through the abdominal wall. Drainage was instituted in all four cases; we feel that it is always better to do cholecystectomies because it is operatively faster, easier to perform and we think, more effective, if most of the pus is aspirated. Cholecystectomized patients had in each case extensive necrosis of the gall bladder and in one case the necrosis was almost total.

The intestinal hemorrhages, diarrhea, poor feeding, purgatives and enemas are listed as in Tables II-A and II-B. Our only survival was that of a patient that came to operation before the third day of rupture and our previous experience in these cases helped us to make an early diagnosis. In the three previous cases, perforation had taken place at least a week or more before, and although the peritoneum had displayed marked resistance to the typhoid bacillus, it was apparent that bile irritation which favored secondary infection made the outlook more severe. We were so aware of these perforations that subsequently we were able to diagnose three cases of acute cholecystites in the course of typhoid fever, and the Medical Service, by early treatment, prevented perforations.

Clinical Description

The diagnosis of peritonitis by intestinal perforation in cases of typhoid fever was made according to the following pattern:

1. A patient with a history of a febrile disease of many days duration (minimum 7 days, maximum 53 days) becomes severely ill in the last few days (3-4 days prior to admission). We only had four cases of perforation that actually reached the hospital alive after the 8, 10, 11 and 15 days respectively, and they all died.

2. Agglutination reactions were positive in the blood for Types O. and H. of E. typhosa, the

titre varying between 1 × 100 and 1 × 500 (2 were positive at a low titre; 3 were negative; and in 4 we could not obtain blood samples).

3. There is intense abdominal pain, marked rigidity—especially in the right iliac fossa—together with fecal vomiting and gastro-intestinal peristalsis; constipation follows a period of diarrhea and there is frequently intestinal hemorrhages.

4. The patient had previously been given purgatives, enemas or both. Poor feeding during and before the present illness occurs.

5. Temperature: usually with hyperthermia of 39°C., but sometimes hypothermia of 35.5° to 36°C.

6. Typical peritoneal fascies, malnutrition, patient looking acutely ill and with signs of long staying in bed.

7. The physical examination reveals the findings noted in three and also marked intestinal distension with tympanity of the hepatic area and dullness at the lower abdomen in most of the cases.

8. Rectal examination shows a contracted sphincter and empty rectum; feeling of free fluid in the peritoneal cavity and the pain previously noted in the right iliac fossa; the intestinal loops are here melted together and very tender.

9. If the patient is left in the sitting position for five to ten minutes, plain X-rays taken subsequently, reveal gas in the subdiaphragmatic region, distended intestines with fluid levels.

10. WBC reveals: always neutrophilia, relative or absolute, even if leukocytosis or leukopenia are present. The more intense the leukopenia the more severe the prognosis.

11. Almost 60% of the cases have had intestinal hemorrhages and diarrhea prior to the onset of the picture of perforation.

The diagnosis of peritonitis due to rupture of the gall bladder from typhoid fever is made when in a patient with this disease, a clinical picture of slowly progressive peritonitis is found. Especially is this so, when this condition is compared with one produced by perforation of the intestines. The pain in perforated gall bladder is less intense, localized to the right hypochondriac region with definite rigidity in this area appearing early. In addition, there is a moderate leukocytosis with relative neutrophilia and a positive agglutination test confirms the diagnosis. Marked abdominal distension and lack of pneumoperiteum are seen even if the X-ray are taken after the patient has been sitting for ten minutes. A picture of a more or less complete occlusion with a great amount of free peritoneal fluid is added to the above findings. Parecentesis abdominis gives a purulent, yellow-greenish fluid, resembling urine sometimes, in which the laboratory easily finds bile pigments; with a typhoid acute cholecytitis the clinical picture is similar to the above, with pain, rigidity and tenderness but no bile can be isolated from the fluid in the abdominal cavity. We stress the point that in a patient with typhoid fever in whom signs of moderate peritonitis are present, the diagnosis of perforated gall bladder has to be kept in mind; in this way an early operation can be life saving.

Operations, Pre and Post Operative Care

The following technic is used in all our cases of a perforated intestine: Drainage of the peritoneal cavity with aspiration of as much pus and fecal matter as possible, without breaking too many adhesions. After that, a simple suturing of the perforation with catgut is done in most instances. In four, intestinal resection with entero-lateral anastomosis was performed when there were several perforations or in the case of just one perforation with extensive surrounding necrosis. Recently, we have been practicing the Witzel's technic of enterostomy when we are unable to reduce distension with Abbott's or Levin's tube; if the distension can be controled with tubes we just close the perforation and in this way the patient's problem is solved. Pre and post operatively sulfadiazine is given subcutaneously in dosage of 0.20 gm. per kg. body weight daily and in fractional doses every 6 to 8 hours. We keep the patients in protein and fluid balance with blood, plasma and glucosalines, giving 50 cc./kg. of blood or plasma daily in accordance with the hematocrit count and the specific gravity of the urine, but above all considering the clinical aspect of the patient. The upper respiratory infections, complicating the operation, are treated with penicillin. Patients are denied any oral feedings for three to five days receiving amino acids intravenously. Gastric and rectal intubation are discontinued when the distension subsides. (A rectal tube is inserted up to the cecum; when possible, guided by the surgeon at operation, into the ileum through the ileo-cecal valve; for this purpose a long Levin's tube is used.)

With technic of operation previously described, we have had 9 survivals in 21 patients with perforation of the intestines: approximately a 43% incidence of cure. With these methods our statistics are constantly improving and in time our mortality rate should decrease. Amongst other things it must be borne in mind that the cases that terminated fatally came to the hospital in extremis with perforations of many days duration. In fact, those who did survive had perforations of less than three days and it is our opinion that the excellent pre and post operative care contributed greatly to the success obtained. The operative procedures may be summarized as follows:

TABLE IV

1. Use every method to combat distension.
2. Avoid reinfection of the peritoneum by closing the perforation, draining it by the Witzel method or with resection and primary latero-lateral intestinal anastomosis.
3. Drainage of the peritoneum.
4. Treatment of the infection with all the available means.
5. Supporting the general condition of the patient as normally as possible.

In connection with rupture of the gall bladder we have already described the technic.
Prognosis can be guided in all cases by the following considerations:

TABLE V

Poor Risk Cases

1. General Condition.
   a) Intense toxic and infectious states.
   b) Marked malnutrition.
   c) Signs of cardiovascular weakness.
2. Peritoneal picture, more than three days.
3. WBC: Leukopenia under 5,000; relative neutrophilia and appearance of young forms (myelocytes).

All of these patients are malnourished before and during illness and have had enemas and purgative. A great number have had diarrhea and intestinal hemorrhages. Twenty-one were under 11 years of age, a fact that is contrary to the opinion that a perforation in typhoid fever is more common in adolescents. It is pertinent to say that the hospital accepts only patients that are under 15 years of age.

The postoperative results were:

TABLE VI

Not Operated On		Operated On	
8		21	
Died	Living	Died	Living
7	1	12	9
85%	15%	57%	43%

From August 1946 on, we have been able to use streptomycin in relatively high dosage, combined with intramuscular penicillin and subcutaneous sulfadiazine not because of the typhoid bacillus but because of the Esch. coli; we have a small series that can not be published yet because it is not complete. Together with the above mentioned, aluminum powder (commonly used in industry) has been used to protect the intestine against adhesions, using it directly over the intestines so they adhere neither with the other loops nor with the abdominal wall, because a perfect cover is formed that protects them very well; in this way the bowel is kept entirely exposed, sometimes for weeks, in the laparotomy wound, until the patient's general condition can bear a major operation.

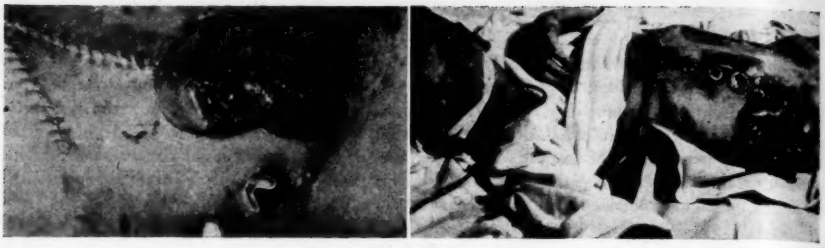


FIG. 1

Wide ileocecostomy. (Second case described.)

After ileo-transverse colon, latero-lateral-anastomosis. Short circuited bowel extroding in lapaotomy wound. (Second case described.)

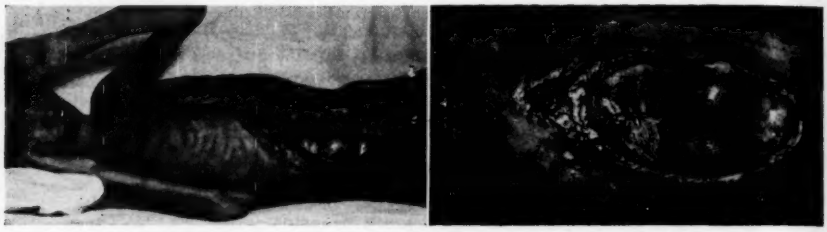
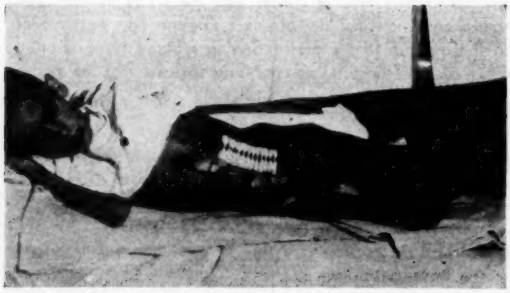
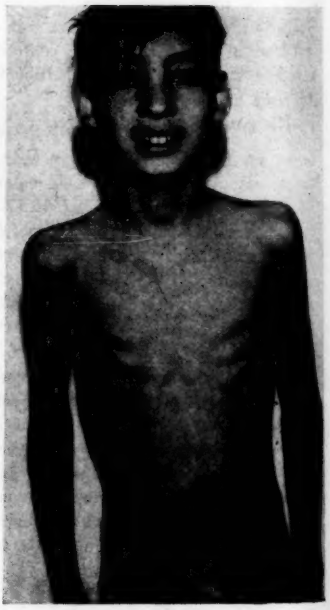


FIG. 2

Ileon and colon widely exposed and covered with aluminum powder for three weeks. (Second case described.)

Close up of patient at left.





Above—Abdominal wall closed after the last operation. (Second case described.)

At right—First case described, two months after he left the hospital.

FIG. 3

Photographs (Fig. 1, 2, and 3) of two patients that were admitted to the hospital in very poor condition and that have undergone a long decompressing ileocecostomy and a wide open laparotomy to drain the pelvis by sucking the pus several times a day are shown. A few days later an open latero-lateral ileo-transverse colon-anastomosis is performed, leaving the short-circuited bowel extruding through the laparotomy wound; weeks later, an ileo-ceco-ascending-colon-resection was made and the abdominal wall closed, benause there was low grade infection of the peritoneum, and no abdominal distention. Bowel movements were normal by this time. We have to stress the importance of keeping the patient as well nourished as possible.

During the days or weeks that the intestines are exposed the patient tends to become practically cachectic; we are not able to draw any conclusions yet, until our new series are completed, probably in the next year, but certainly our statistics are improving. These two cases are shown now just because we consider them of interest in the treatment of typhoid fever perforation cases.

Conclusions

1. Intestinal perforation due to typhoid fever is frequent among children (7.22% of all the cases of typhoid.)
2. Perforations of the intestines and rupture of the gall bladder in typhoid fever must always be operated.
3. In order to improve the statistics, good pre and post operative care is essential, along with expert surgical technic which must provide drainage of the peritoneum, avoidance of reinfection and of abdominal distension.
4. Prognosis is in direct ratio to early operation.
5. Malnutrition, intense toxicity and infection with marked leukopenia, combined with a diagnosis of intestinal perforation or rupture of the gall bladder in typhoid fever, make the prognosis a fatal one.

Summary

The experience at the Hospital Infantil of Mexico City in dealing with intestinal perforations and rupture of the gall bladder in typhoid fever is presented.

Four hundred and fifty-seven cases of typhoid fever among 15,688 general admissions in 3 years, with 29 cases of intestinal perforations and 4 ruptured gall bladders form the basis of this report. Twenty-one were operated on, with a survival of 9 (43% survivals with operation), 8 were not operated on. Seven of these died (85% mortality). Of four cases of rupture of the gall bladder all were operated on and one survived.

Dr. Clifford Sweet, Oakland, Calif., **The Child as a Surgical Patient:**

I. Introduction

Within the limits of this very brief paper an attempt will be made to state some of the principles which will be helpful to anyone who must carry infants and young children through surgical procedures. For example, the child's inability to survive long continued dehydration and starvation is emphasized but the details of parenteral feeding will not be given.

Administration of parenteral fluids:

When one must care for a child who has been badly depleted before he comes to the surgeon or who must undergo a prolonged operation followed by days during which no fluid or food can be taken by mouth, he must make every effort to supply his needs for water, electrolytes, calories, protein and vitamins by parenteral routes. Every surgical team that cares for infants should have a member who can give a continuous intravenous drip. When no such help is available much can be done by hypodermoclysis to supply ample water and electrolytes as well as some calories in the form of glucose and protein as amino acids. Except in the hands of a skillful attendant, the veins should be saved for transfusions of blood and plasma.

Fluids given by hypodermoclysis should be injected intramuscularly rather than subcutaneously. They are absorbed from the muscles in about half the time required for subcutaneous absorption and cause much less pain when placed in the deeper tissues.

Solutions should be given by gravity to children of all ages and should not be forcefully pushed

in with a hypodermic syringe. The needles for injection by gravity can be strapped in place and left there for days. An attendant then clamps off the connected tubing before the tissues become greatly distended and removes the clamps as soon as sufficient absorption has taken place.

There is danger in giving the patient too much sodium chloride and it is possible to give him too much water. Fortunately, however, a fairly wide margin of safety for both salt and water is provided by the function of intact kidneys while the anuric differs from other patients in an important respect; water and not salt is the important factor in edema formation. The normal patient is better off with a moderate excess of salt and even a considerable one of water than he is with a grave deficit of either. The appearance of edema of the scrotum, the labia or over the tibia is a reasonably safe sign of an excess of salt or water if one must work without the help of frequent accurate laboratory analysis such as the CO_2 combining power, chloride and protein levels of the blood. On the other hand, any sign of approaching paralytic ileus may well indicate a low chloride and/or protein blood level. Also since all patients with peritoneal infection must have an inlying gastric suction tube, allowance must be made for the salt which is thus constantly removed from the stomach.

II. Pre-operative Care

New born infants with a congenital malformation that will cause death within a short time unless it is corrected should be operated upon as soon as possible after birth. Operation should precede any serious loss of body fluids, electrolytes and protein and all of the advantages of parenteral feeding be used to support the patient during operation and through the post-operative period. Examples of the need for such prompt operation are intestinal obstruction in any form, tracheoesophageal fistula and diaphragmatic hernia.

Infants and children who have for any reason become dehydrated, have a low electrolyte level or in a state of semi-starvation from lack of carbohydrate and/or protein should have these levels raised to the highest practical point by parenteral feeding and then be operated upon without further loss of time. Parenteral feeding at its best is an imperfect substitute for oral feeding. If cannot, at present, supply all of the patient's needs and after a time cannot by itself sustain life. If, therefore, needed surgery is not done while there is still a sufficient margin of parenteral feeding left unused to carry the patient through the post-operative period until mouth feeding can be resumed, death will ensue. Any patient who is allowed to use all the sustenance which parenteral feeding alone can bestow will quickly go into metabolic failure from which he cannot be rescued unless he can take additional food by mouth. For example, an infant with pyloric stenosis should be operated upon as soon as parenteral feeding has restored his metabolic balance to a level that will carry him safely through the operation and the post-operative period.

When the child's reserves of fluid, electrolytes and food have been depleted by vomiting and/or diarrhea and starvation in the presence of an acute infection, he should then have his nutrient levels improved by parenteral feeding while at the same time the infectious process is vigorously attacked by quickly attained, sustained blood levels of sulfonamide and/or penicillin. If the focus of infection is such that a surgical attack is indicated, this should be carried out as soon as judgment indicates that the patient can reasonably withstand the operation. For example, a ruptured appendix should be removed while the patient's condition is definitely improving under a well-planned course of parenteral fluids, electrolytes, whole blood when indicated, and an adequate blood level of sulfonamide and penicillin.

When the child is conscious and old enough to remember his fear upon entering the operating room, he should be given a sufficient dose of barbiturate or avertin by rectum to reduce these fears to a minimum. Either should be given an hour or more before the time set for operation and avertin is contraindicated in the presence of previous renal damage.

Opiates should not be given to infants pre-operatively when an inhalation anesthetic is to be used. They should be given to young children (under six years) in small doses only when needed for the relief of severe pain. Even when given for relief of pain they should be given an hour or more before the induction of anesthesia is begun. The respiratory center of the child is easily depressed and when its function falters or ceases it is not as certainly or as easily restored as it is in an older patient.

III. Post-Operative Treatment

Post-operative treatment for the child has the following objectives: 1. To maintain his fluid, electrolytes, protein, vitamin and caloric body levels well elevated until feeding by mouth can be

resumed; 2. To prevent the occurrence of pain; 3. To prevent vomiting; 4. To prevent or to reduce distention of the gastro-intestinal tract; 5. To combat present or threatened infection with chemo and antibiotic therapy.

The problems of post-operative treatment divide themselves naturally into two classes. The first concerns the child who is in good condition and whose operation has only a slight or moderate effect upon his state of well being and allows an early resumption of mouth feeding.

The second, much more difficult than the first, concerns those children who 1. have perhaps already suffered considerable metabolic damage before surgery is contemplated, 2. have an illness and/or an operation that prevents any mouth feeding for many days after operation, 3. have an infectious process in their bodies which must be overcome during their post-operative period of recovery. Any or all of these conditions may be present singly or in all possible combinations in a single child.

For those in the first class, as for example, the removal of an unruptured appendix, a herniorraphy or a pyloric stenosis with the patient in good metabolic balance, no serious nutritional problem presents itself. In fact, after such operations when fluids can be given by mouth within 48 hours one can safely content himself with attention to the water balance only. However, the water intake must be adequate and any unnecessary water loss must be prevented.

Nearly all of these children, except very young infants, can be given the greater part if not all of their needed water by rectum as tap water. The patient who receives adequate water by rectum is not plagued by thirst and is therefore content to let his stomach rest until its tone has improved sufficiently to take fluids without nausea or vomiting. The tap water is given in doses of 100 to 400 cc. at four-hour intervals through a small well-lubricated catheter attached to an open funnel. The catheter is plainly marked 2½ inches from its terminal end and is never inserted beyond this mark. The use of the rectal route for water is efficient, painless, does not require restraint in bed, is without cost to the patient, and ward attendants and can be easily taught to use it expertly. It can be continued, if no salt or glucose is added during the first 48 hours after operation or until the patient can drink freely without discomfort. Tap water by rectum is easily retained while the patient is under the influence of the alternating doses of an opiate and a barbiturate which should be given routinely during the first 48 hours to control pain and prevent vomiting.

Water with its accompanying electrolytes is lost rapidly and unnecessarily from the body by vomiting and from sweating in response to excess heat or the activity caused by uncontrolled pain.

Vomiting, except in the patient who has an obstructed or distended gastro-intestinal tract and pain can be controlled simultaneously by adequate alternate doses of an opiate and a barbiturate. Pantopon has been the most satisfactory opiate following major surgical procedures for several years past. Sodium amytal has been found to be a very satisfactory barbiturate because of its prolonged action. The opiate is given as soon as the patient arouses sufficiently to be in pain followed by the barbiturate when the opiate begins to wear off. Each is repeated alternately only when needed usually until 48 post-operative hours have passed. When given in this manner, the effect of each is prolonged by the other. Very frequently a single dose of the opiate followed in three or four hours by a dose of sodium amytal by rectum will keep the patient quiet and comfortable for ten or even twelve hours. Unbroken capsules, containing sodium amytal or any other barbiturate, when lubricated with any water soluble lubricant do not cause any delay in the absorption of their contents from the rectum. The larger doses given by rectum have an effect lasting about 50% longer than the corresponding mouth dose and can easily be given to a child of any age and state of consciousness.

Post-operative orders for a six-year-old child following an appendectomy or a herniorraphy are:

1. Pantopon 0.01 gm. by hypodermic as soon as in pain. (Morphine 0.008 gm. or codein 0.065 gm. may be used is preferred.

2. As soon as the pantopon begins to wear off, give sodium amytal 0.25 gm. by rectum. Nembutal 0.13 gm. may be given instead of sodium amytal if one wishes.

3. Repeat the opiate and the barbiturate alternately as needed to keep the patient comfortable.

4. Tap water 250 cc. by rectum every four hours.

5. Catheterize if unable to void before the bladder becomes distended.

For the control of post-operative or any pain that might be equally severe, the following schedule is safe and effective:

Age	*Morphine*	*Pantopon*
2 years	0.0006 gm.	0.007 gm.
6 years	0.008 gm.	0.01 gm.
10 years	0.01 gm.	0.015 gm.
14 years	0.015 gm.	0.02 gm.

A conservative dose of sodium amytal by rectum is 0.03 to 0.045 gm. for each year of the patient's age. All of the above methods can be equally well used for the treatment of patients of the second class with the addition of parenteral feeding, chemotherapy and antibiotic therapy.

Patients with a distended gastro-intestinal tract should always have an inlying gastric tube attached to a Wangensteen suction apparatus. The material removed from the stomach should be caught in a separate bottle in order that its amount can be estimated with sufficient accuracy to replace it by parenteral water and sodium chloride. They should also be placed in an oxygen tent containing a high oxygen content—up to 95%—if possible. The oxygen supplies the patient's needs with greatly reduced respiratory effort on his part and thereby often transforms a struggling uncomfortable child into one who sleeps and rests. Also, the distended loops of bowels are filled with swallowed air from which the oxygen content is readily absorbed leaving behind the considerable nitrogen content of air. When the patient is in a nearly pure oxygen atmosphere, the nitrogen in his bowel is gradually displaced by the readily absorbable oxygen and intestinal distention is thereby reduced.

Children should not be allowed to suffer needless pain and vomiting following tonsillectomy. If they were spared the post-operative discomforts which follow this operation, our psychiatric colleagues could not so often and perhaps justifiably attribute our patients' emotional upsets to the removal of their tonsils and adenoids.

The post-operative orders for a patient whose tonsils and adenoids have been removed should be:

1. Codein 0.024 gm. at three years to 0.048 gm. at five years when in pain.
2. Sodium amytal 0.13 to 0.2 gm. by rectum as soon as codein wears off. May be repeated at night if needed.
3. Glucosulfamyrazine 4 cc. at 2 p.m. and 6 p.m. and every six hours thereafter. The sulfamyrazine to be continued at six-hour intervals night and day at home for four or five days.
4. Food and drink as usual.

The codein and amytal will make the first 24 post-operative hours relatively comfortable and reduce vomiting to a minimum. The sulfamyrizine will have a like effect upon the usual discomfort of the following days and when the throat is seen a week later it will be almost completely healed. Also, the continued use of the sulfonamide reduces the size of the post-operative slough from the tonsil fossae so greatly that the much dreaded post-operative bleeding on the seventh to tenth day following operation will all but disappear.

Sodium sulfadiazine in five percent solution can be given subcutaneously without local irritation. The initiation dose should be 0.15/kg. body weight and double this amount during each 24 hours divided into four doses. Since fluid is being given and excreted in large amounts it may be necessary to give larger amounts in order to maintain an effective blood level. As a matter of convenience sodium sulfadiazine may be added to any fluids given by clysis in 2 to 6 gm. amounts. When given in this latter manner the blood level is more difficult to control and may arise to twenty or more mg. per 100 cc. of blood—fortunately, with rare if any reactions to the sulfadiazine.

Some surgeons place their reliance upon penicillin alone for the treatment of peritonitis, but I have found the combined use of sulfadiazine and penicillin more efficacious than either alone. Some earlier cases whose progress was not satisfactory even in the presence of an adequate sulfonamide blood level made dramatic improvement when penicillin was given in addition.

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*Dr. M. Digby Leigh, and Dr. M. Kathleen Belton, Vancouver, Canada,** **Pediatric Anesthesia:**

Pediatric anesthesia has created more and more interest as pediatric surgery continues to progress. Operations previously performed with a great deal of risk are now attempted with more confidence

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* From Vancouver General Hospital.

of survival of the patient. No small measure of this is due to the advancement of anesthesia. Several of these improved technics and agents have been adapted successfully to infants' and children's anesthesia. Considerable aid has been obtained from the book "Physiology of the Newborn" by Clement A. Smith who has outlined many of the physiologic differences between infant and adult. For example, in the infant there is a rapid heart rate, lower blood pressure, faster circulation time; and then again there is a tendency to irregular respiration, rapid respiratory rate, comparatively small tidal flow of air, all of which have to be taken into consideration. In addition, one must keep in mind the tremendous changes which occur in the first part of life. Even in the first year the average developing infant triples its birth weight. These variations from the adult have delayed the advancement of pediatric anesthesia but gradually the difficulties are being surmounted and anesthetic agents and technics which have been employed successfully in adult anesthesia are finding their way into the pediatric field. Inhalation, intravenous, rectal anesthesia, and anesthesia with local agents which includes spinal, are established as recognized technics in many pediatric centers.

Preanesthetic Medication

For some time controversy has raged around the problem of preanesthetic medication. Anesthesiologists have been ready to admit the many advantages which accrue from preanesthetic medication in adult anesthesia; namely, removal of apprehension, reduction in amount of anesthetic agent, reduction of obstructive secretions in the respiratory tract. These same advantages can be obtained in infants' and children's anesthesia with the added advantage of a decrease in the exhaustive respiratory rate. At times, under ether anesthesia, a respiratory rate of over 100/min. may occur. This is definitely exhaustive and can be controlled to some extent by the morphine in the preanesthetic medication. As an example, the child of normal weight, age seven months, can be given 0.5 mg. of morphine and 0.1 mg. scopolamine an hour before operation.

Pediatricians on the whole have condemned the use of morphine in infants. This condemnation has been due largely to unfortunate events such as depression of respiration and in some instances even respiratory arrest. For this reason, the anesthesiologist has reduced the dose of morphine in infants. In addition, he has taken great pains to insure that the proper dosage is administered. In most hospitals the smallest dose of morphine available is 5.0 mg. If a dose such as 0.5 mg. is to be given, the 5.0 mg. should be diluted in 5 cc. of distilled water. This mixture should be shaken thoroughly and 0.5 cc. of the mixture administered. If the nurse attempts to measure this drug in a smaller dilution there will be considerable inaccuracy in the dose of morphine given.

To give some idea of the dosages of morphine and scopolamine which may be employed safely as premedication in infants and children, the following table is suggested as a guide.

PREMEDICATION—HYPODERMICALLY

Apparent Age	Weight (kg.)	Morphine (mg.)	Scopolamine (mg.)
Up to 2 mo.	3.7–4.5	0.12	0.1
2–3 mo.	4.5–5.4	0.17	0.1
3–4 mo.	5.4–6.4	0.26	0.1
4–7 mo.	6.4–7.2	0.4	0.1
7–11 mo.	7.2–9.0	0.5	0.1
11–18 mo.	9.0–11.0	0.6	0.1
18 mo–2 yr.	11.0–12.5	0.9	0.13
2–3 yr.	12.5–13.7	1.0	0.13
3–5 yr.	13.7–18.0	1.2	0.13
5–8 yr.	18.0–25.0	1.7	0.2
8–10 yr.	25.0–30.0	2.5	0.2
10–12 yr.	30.0–37.0	3.0	0.3
12–14 yr.	37.0–40.0	5.0	0.4
Adult	40.0 kg. and up	8.0–15	0.4–0.6

However, patients who have been given morphine and scopolamine premedication often have a

slower induction of anesthesia than if morphine alone, or morphine and atropine combined, had been administered. Another table serves as a guide for morphine an atropine administration hypodermically.

Apparent Age	Weight (kg.)	Morphine (mg.)	Atropine (mg.)
Up to 2 mo.	3.7–4.5	0.11	0.15
2–3 mo.	4.5–5.4	0.17	0.15
3–4 mo.	5.4–6.4	0.26	0.15
4–7 mo.	6.4–7.2	0.4	0.15
7–11 mo.	7.2–9.0	0.5	0.15
11–18 mo.	9.0–11.0	0.6	0.15
18 mo.–2 yr.	11.0–12.5	0.7	0.2
2–3 yr.	12.5–13.7	1.0	0.2
3–5 yr.	13.7–18.0	1.2	0.2
5–8 yr.	18.0–2.5	1.7	0.3
8–10 yr.	25–30	2.5	0.3
10–12 yr.	30–37	3.0	0.6
12–14 yr.	37–40	5.0	0.8
Adult	40 and up	8–15	0.8

Large doses of morphine produce considerable vomiting in the child. Recently in error a child of six years of age was given 10.0 mg. of morphine; although no operation was performed and no anesthetic administered, that child vomited for 24 hours. On numerous other occasions we have administered intravenously large doses of morphine and often it has been followed by frequent and prolonged vomiting. However, there are occasions when the anesthesiologist deliberately administers large doses of opiates. As a specific example we cite the operation for tetralogy of Fallot where the anesthesiologist uses the large doses of morphine in order to secure greater control of pulmonary ventilation.

Atropine or scopolamine may be used alone purely for their drying effects.

Barbiturates may be added to any of the above combinations on occasion especially if the patient is to have spinal or local anesthesia.

Anesthetic Agents and Technics

The inhalation technic is still the most favored method of anesthesia in children. The reason for this is that from a psychologic point of view it is necessary in most cases to keep the infant or child quiet with some general depressant. There are several types of inhalation anesthesia which have a wide use in the pediatric field. Open drop ether is still the safest for the casual anesthesiologist and has a wide application in the hands of the specialist.

Open drop ether is usually begun either with vinethene or ethyl chloride. Both have disadvantages: the former may produce convulsions, the latter cardiac arrest. However, by including a barbiturate such as seconal in the preanesthetic medication, seldom will convulsions be seen with vinethene. Ethyl chloride has had a widespread use and seldom causes cardiac difficulties in the hands of the expert.

In the administration of open drop ether it has been found advantageous to flow oxygen 1 or 2 l./min., under the mask. This raises the oxygen concentration of the inspired air and lowers the carbon dioxide.

Although ethyl chloride and open drop ether still have a wide sphere in anesthesia for children, yet with certain modifications, all the inhalation agents and technics employed in adults can be used with the same benefits in pediatric anesthesia. It is beyond the scope of this paper to discuss these modifications in detail. Anesthetic agents such as nitrous oxide, ethylene, and cyclopropane disturb the body much less physiologically and biochemically than ether. To quote a few instances witness the increased concentration of the blood, the elevated blood sugar, and the metabolic acidosis which occurs soon after the commencement of an ether anesthesia. These disadvantages are not present when less toxic agents are used.

At this point it might be mentioned that there has been a growing tendency towards the use of the endotracheal tube. This is particularly true in operations around the head, in the throat or in the thorax. For example, in intracranial operations where the head is inaccessible to the anesthesiologist during the operation, an endotracheal tube has been found advantageous even in the newborn. Likewise, in cleft lip and palate operations and tonsilectomies, where it is essential to maintain a clear airway and to prevent the blood from entering the trachea, an endotracheal tube is a distinct benefit. This allows for deliberate meticulous surgery, an essential factor in the restoration of the normal architecture of a lip or a palate. There is also the advantage of a reduction in the dead air space which keeps the inhaled atmosphere rich in oxygen and low in carbon dioxide. However, all methods have some disadvantages and the endotracheal technic is no exception; for occasionally laryngitis occurs for one or two hours or even longer postoperatively. However, it is felt the advantages far outweight the disadvantages.

Likewise, in intrathoracic surgery it is essential to maintain adequate ventilation of the lungs. This can be maintained more consistently through an endotracheal tube.

Intravenous Anesthesia

Although it has been said that the intravenous technic has no place in infants' or children's anesthesia, this statement applies more particularly to the inexperienced. Intravenous pentothal sodium has been used in anesthesia combined with some other technic. It also has been used to control convulsions. The main difficulty is a technical one, that is the venipuncture. However, if a hypodermic needle is used venipuncture is not too difficult. Nevertheless, one should always be prepared for artificial respiration with oxygen and it can hardly be considered an office procedure. At times curare is given intravenously either to relax the abdominal muscles for surgical procedure or to relax the muscles of the jaw or thorax for removal of foreign bodies in the bronchial tree. Again, this procedure should never be undertaken outside a hospital and means of artificial respiration should be at hand.

It is important to remember that large doses of these intravenous drugs should be avoided since prolonged depression of respiration may occur. In other words, they are used as adjuncts to some other anesthetic technic.

Rectal Anesthesia

One of the most popular and widespread methods of inducing anesthesia in infants and children is through the rectum. The anesthetic agents such as avertin, pentothal, seconal, paraldehyde, ether-in-oil, have been employed. These agents may be administered in the ward and the child can go to sleep quietly and comfortably in his own room. Obviously there is little psychic disturbance with this technic. However, it has some disadvantages since it is difficult to determine the proper dosage, and it lacks controllability. In addition, it requires considerably more time. In spite of this it will always hold a prominent place in the field of pediatric anesthesia.

Seldom is rectal anesthesia used alone since agents like avertin and the barbiturates have little pain-relieving power and must be combined with such agents as ether, cyclopropane or nitrous oxide, which are noted for their analgesic properties.

Anesthesia with Local Agents

Although anesthesia with local anesthetic agents such as procaine and pontocaine has not a widespread use; nevertheless, they can be employed to advantage in some cases. For example, the patient with acute appendicitis with a metabolic acidosis from starvation and vomiting, will have no increase in acidosis when spinal anesthesia is employed. In contrast, ether anesthesia will aggravate the condition of metabolic acidosis; and on occasion such patients have developed fatal ether convulsions during the operation. Occasionally prolonged spinal anesthesia has been employed for plastic operations of the lower extremities. At times extensive abdominal operations have been performed to advantage under spinal anesthesia. One such case was that of a little boy who between the age of five and ten years had five major abdominal operations for intestinal obstruction. This child vomited copiously and for a long time following ether anesthesia. Because of this he preferred spinal anesthesia. Two of these operations lasted over four hours and were performed under continuous spinal. Often these patients must be kept quietly asleep with nitrous oxide or intravenous pentothal in small quantities.

These are occasions when even nerve block has been used to advantage. This is particularly true when a patient has had a meal recently or has had an accident immediately following a meal. It is hazardous to give these patients a general anesthetic since they may vomit and aspirate solid food into their lungs and have a sudden exit.

Such procedures as brachial plexus block, wrist block and field block may be used. These particular technics have the added advantage that there is better circulation with less edema and pain in the injured extremity following operation. The blocks apparently produce a sympathetic paralysis and, therefore, dilatation of the vessels in the extremity.

SUMMARY

It has been pointed out in this paper that most technics which are employed successfully in adult anesthesia can be used to a large extent with the same advantages in infants and children. Therefore, in pediatric centers one finds preanesthetic medication, inhalation, intravenous, rectal, spinal and regional anesthesia employed safely and with advantage to both patient and surgeon.

Dr. Frank B. Ingraham, Boston, Mass., **Craniosynostosis** (Surgery: in press.):

Dr. John W. Duckett, Dallas, Tex., **Surgical Aspects of Congenital Cardiac Anomalies:**

A new field of surgical therapy is developing which challenges the technical skill and ingenuity of the surgeon and the diagnostic acumen of the internist.

The 1937 edition of "Heart Disease," by Paul D. White, contained the statement that "there is no curative treatment, surgical or medical, for congenital cardiac defects." So varied and complex were these defects, and so futile had been all attempts at treatment, that clinicians had little interest in making accurate anatomic diagnoses. One outstanding contribution was made by Maude Abbott, who in 1936 published a classification of congenital heart disease based on clinical and autopsy studies in 1,000 cases. These cases are divided by Dr. Abbott into three groups, based on presence or absence of cyanosis. The first is the "acyanotic group," without abnormal communications or shunts. Most frequently found in this group are aortic or subaortic stenosis, right aortic arch or dextrocardia, and coarctation of the aorta. The second is the "usually acyanotic group" in which arterial blood enters the pulmonary circulation through a shunt. Representative of this group are interventricular septal defect, interauricular septal defect, and patent ductus arteriosus. The third is the "cyanotic group" in which quantities of venous blood enter the systemic circulation. Most important in this group are pure pulmonary stenosis, tetralogy of Fallot, and Eisenmenger's complex. In the tetralogy of Fallot there is stenosis or atresia of the infundibular portion of the pulmonary artery, dextroposition of the aorta, interventricular septal defect, and right ventricular hypertrophy. The Eisenmenger complex includes an interventricular septal defect, dextroposition of the aorta, but a normal or dilated pulmonary artery.

During the past ten years successful operations have been developed for the correction of one of the defects in each of Abbott's three groups. In 1938 Robert Gross of Boston performed the first successful ligation of a patent ductus arteriosus. In October 1944, Clarence Crafoord of Stockholm, Sweden, was first to correct a coarctation of the aorta. In November 1944, Alfred Blalock, of Baltimore, relieved cyanosis in a patient with the tetralogy of Fallott by constructing an artificial patent ductus arteriosus.

PATENT DUCTUS ARTERIOSUS

The diagnosis can be made with certainty in almost every case. Severity of symptoms varies roughly with the size of the ductus. Symptoms are absent or minimal in early life becoming more apparent as cardiac failure or other complications appear. Of these, subacute bacterial endarteritis is most serious, being responsible for thirty percent of deaths in patients with a patent ductus. Since much blood is diverted from the systemic circulation, growth is usually retarded.

The most characteristic physical finding is the heart murmur, typically a continuous or "machinery" murmur best heard in the left second and third interspaces near the sternal border and usually accompanied by a palpable thrill. The pulmonic second sound is increased in intensity. The systolic blood pressure is increased, and the diastolic decreased, resulting in a wide pulse pressure. X-ray studies

of the heart may be useful though they may show no abnormalities. Characteristically, the heart is shown to be slightly enlarged to the left, and there is a distinct enlargement of the pulmonary artery segment. The lung fields show vascular markings to be increased, and on fluoroscopy there may be visible pulsations in the lungs—the so-called "hilar dance."

The electrocardiogram may be normal though usually there is slight left axis deviation.

Operative treatment of a patent ductus undertakes to eliminate the arteriovenous shunt by ligation, division, or excision of the ductus. The original operation performed by Gross was simple ligation, later supplemented by the addition of cellophane beneath the ligature to stimulate fibrous proliferation. Because of a small number of recurrences, Gross changed his procedure to division of the ductus and closure of the cut ends by suture. Crafoord has gone even further and practices complete excision of the ductus with closure of the defects by suture of the walls of the aorta and pulmonary artery. Many still consider ligation adequate and the added dangers of division or excision unjustified. Over six hundred operations for patent ductus have been reported, and undoubtedly many more have been performed. The mortality is 5% among all cases reported but probably no more than 2% in the hands of the most experienced surgeons. Mortality is greatly increased in the older age group and in the presence of subacute bacterial endarteritis.

In consideration of the relatively low operative mortality especially in childhood and conclusive evidence that life expectancy is decreased in those afflicted with this lesion, the belief is now widespread that operation should be done in all children between the ages of 3 and 10 years when the diagnosis is definitely established.

Coarctation of the Aorta

The "adult type" in which there is a narrowing of the lumen of the aorta at or just below the insertion of the ductus lends itself to surgical treatment, while the "infant type" in which a longer segment of the aorta is involved, usually ends fatally shortly after birth. With the adult type, collateral circulation can be developed which allows survival in many cases to adult age. There may be no symptoms during childhood, but eventually evidences of cardiac failure or of hypertension appear. Hypertension occurs in the head and upper extremities while blood pressure in the lower extremities is low or even unrecordable. Enlargement of collateral arteries may be visible or palpable in the back and the axilla, and a vascular murmur is often heard in the back. A loud systolic murmur is heard at the base of the heart.

X-rays may show characteristic notching of ribs caused by pressure from enlarged and tortuous intercostal arteries. The heart shadow is at first normal but later shows enlargement to the left. Angiocardiograms may demonstrate the stenotic area or at least the dilated arteries.

The average age reached by patients with coarctation of the aorta is thirty-two years. Most will succumb to heart failure. Some deaths are due to rupture of the aorta, cerebral hemorrhage or bacterial endarteritis. Although the operation is more dangerous than that for treatment of patent ductus arteriosus, it should probably be advised for all patients between the ages of 6 and 16 years whenever the diagnosis has been definitely made. Before six years, collateral circulation is hardly adequate to allow clamping of the aorta for sufficient time to permit resection of the stenosed segment and anastomosis. After 16 years, the aorta begins to develop atheromatous plaques and rigidity of the wall which may prevent successful anastomosis. Although the first successful operation for coarctation was done by Crafoord in 1944, Robert Gross independently and without knowledge of Crafoord's work, performed a similar operation shortly afterward. By December 6, 1947, Gross had operated on 40 patients for coarctation with five deaths. Only a few cases have been reported by others.

Tetralogy of Fallot

Cyanosis is noticed soon after birth and gradually increases in severity for the first few years. The cyanosis is produced partly by mixture of venous and arterial blood through a high interventricular septal defect associated with an aorta displaced toward the right so that it overrides the septal defect, and partly by stenosis or atresia of the pulmonary artery resulting in decreased blood flow to the lungs and consequent poor oxygenation.

Symptoms are mainly due to anoxia from low oxygen saturation of the blood. In infancy there may be attacks of loss of consciousness or convulsions from cerebral anoxia. There is usually definite retardation in growth and development; attempts to walk are delayed and later there is low tolerance

to exercise, not so much from dyspnea as from fatigue. A characteristic trait of children thus afflicted is "squatting" to rest at frequent intervals.

Physical signs are striking. There is cyanosis of lips and nail beds, intensified by exertion or crying. Conjunctivae and sclerae are injected. Fingers and toes become clubbed at an early age. A systolic murmur is heard at the base of the heart, and occasionally a thrill. Blood examination shows marked polycythemia, RBC often reaching 8 or 9 million cc. with correspondingly high hemoglobin reading.

In addition to the clinical picture X-ray findings are indispensable in arriving at a correct diagnosis. The heart is normal in size and may be normal in shape but usually shows a characteristic concavity in the region of the pulmonary artery segment. This combined with a slightly raised apex indicating right ventricular hypertrophy produces the typical "boot shaped" heart which is practically diagnostic. In addition the small size of the pulmonary artery is shown by an abnormally large "pulmonary window" as seen in the left anterior oblique view of the heart. An important X-ray finding is unusual clearness of the lung fields and absence of visible pulsations in the lungs. In about 20% of cases there is a right sided aortic arch.

The electrocardiogram regularly shows right axis deviation.

No curative treatment is available for cyanotic heart disease as for patent ductus arteriosus and coarctation of the aorta. The brilliant work of Taussig and Blalock, first on experimental animals and then on human subjects, has proved, however, that low oxygen saturation of the blood can be raised significantly by increasing blood flow through the lungs, and the symptoms of anoxia can be completely relieved or at least improved. This is accomplished by the construction of an artificial ductus arteriosus, formed by anastomosis of a branch from the aorta to one of the pulmonary arteries. The operation as designed by Blalock has a number of possible variations depending on the side on which the aorta descends, the size of the pulmonary artery and the availability of a systemic vessel. The most efficient anastomosis is usually that made with the end of the subclavian branch of the innominate artery to the side of the right or left pulmonary artery.

By December 1, 1947, Blalock had operated on 560 patients with cyanotic heart disease. The overall mortality was 17% in his cases and has been somewhat higher in small series now being reported by other surgeons. Willis J. Potts of Chicago is performing another type of operation for this condition, consisting of side to side anastomosis of the aorta and pulmonary artery. This is made possible by the use of an ingenious clamp which isolates a segment of the wall of the aorta while allowing free flow of blood through the aorta.

Since patients requiring these operations are poor surgical risks, the mortality is necessarily high. The ultimate outlook is uncertain for these patients since the addition of an artificial patent ductus to the complexity of congenital abnormalities adds extra strain on the left ventricle. There is no doubt, however, that most patients show marked diminution in cyanosis, increase in arterial oxygen saturation, and relief of symptoms very soon after operation. Since these patients are all physically handicapped, many to the point of invalidism, restoration to normal or near-normal activity fully justifies the risk of operation regardless of what the future may have in store for them.

The author has operated on 10 patients for patent ductus arteriosus using the multiple ligation described by Blalock in all cases. Seven of these were children, of whom one died of post operative pulmonary complications. Three were adults of whom two died, one of acute cardiac decompensation, and the other of hemorrhage one week after operation.

Twenty-five children with cyanotic heart disease have been operated on. In 22 the Blalock anastomosis operation was completed. Five of this group died, as did one of the three in whom an anastomosis was found impossible. The total mortality was 24%. Improvement was shown by every child who survived the anastomosis, and in most the results were striking.

4105 Live Oak Street

*Dr. F. R. Wilkinson, Toronto, Canada,** **The Diagnosis and Early Treatment of Acute Hematogenous Osteomyelitis in Children:**

Today, acute hematogenous osteomyelitis need not be a fatal or crippling disease of childhood. Early and adequate treatment with penicillin and sulphadiazine aborts the disease with minimal

* From the Department of Surgery, University of Toronto, and the Hospital for Sick Children.

bone change and lowers the mortality almost to zero. At the Hospital for Sick Children in Toronto we no longer operate during the acute stage of the illness; indeed, have not done so for the past six years. Osteomyelitis can kill or cripple if a diagnosis is not made soon after the onset. The results will continue to improve when more patients consult the doctor promptly, and when more doctors are alert to the early symptoms of the disease.

Diagnosis

The diagnosis should be made within 24 hours of the onset and the patient sent to hospital. Every case of severe pain near a joint with a point of maximum tenderness near the end of the bone in a growing child should be considered as evidence of osteomyelitis until proved otherwise. If accompanied by toxemia, rapid pulse, high temperature, and a high leukocyte count the diagnosis is reasonably certain. X-rays are of no value at this stage and should not lull one into a false sense of security. The earliest X-ray change is usually seen about ten days after the onset and consists in a reduction of density due to bone absorption. Several days later areas of destruction and of subperiosteal new bone formation are visible.

Differential Diagnosis

In *acute suppurative arthritis* the signs are primarily in the joint and not at the metaphysis. There is an early effusion; muscle spasm is more marked; and limitation of motion greater. Aspiration of the joint and examination of the fluid by direct smear and culture will settle the question. *Acute rheumatic fever* may cause confusion but the onset is more gradual, the pain less severe and usually more than one joint is involved. Valuable time should not be wasted in giving salicylate as a therapeutic test. In *erysipelas* the skin is red and shiny with a raised edge. *Cellulitis* may suggest osteomyelitis but the swelling and redness appear earlier. The pain is not so intense and the toxemia is less. *Ewing's tumor* is sometimes mistaken for osteomyelitis. The onset may be quite acute with pain, fever, and leukocytosis. The pain is usually intermittent at first. The fever is not so high and in the X-rays there is a diffuse rarefaction toward the center of the shaft and extending for a considerable area. Later there is onion-skin subperiosteal deposition of new bone and finally widespread destruction of bone. *Infantile scurvy* causes hemorrhages beneath the periosteum resulting in pain, fever, and swelling with marked subperiosteal new bone formation. In the past six months, I have seen two cases of osteomyelitis diagnosed as poliomyelitis. There should be no difficulty if one remembers that osteomyelitis does not occur in the polio season.

I have spent some time on the differential diagnosis because I want to emphasize again the importance of making an early diagnosis of osteomyelitis. It makes very little difference if a patient with rheumatic fever is given penicillin for a day or two, but it makes a very great difference indeed both to life and to limb if a patient with osteomyelitis is given aspirin instead of penicillin.

Prognosis

Osteomyelitis in children is a dangerous disease. Before the sulphonamides and penicillin at the Hospital for Sick Children there were 140 deaths in 674 cases, a mortality of 20.7%. From January 1940 to December 1947 there have been 177 with 7 deaths, a mortality of 3.9%. Autopsies were done in all seven fatal cases. In all death was due to septicemia with multiple pyemic abscess. There have been no deaths since August 1944. Staphylococcal infection is the most serious type both as regards life and bone destruction.

The nearer the trunk the affected bone and the younger the child the graver the prognosis.

Treatment

Since the spring of 1942 following the lead of our late surgeon in chief, Dr. D. E. Robertson, we have not been operating upon patients with acute hematogenous osteomyelitis.

On admission the child is given a sedative; glucose and saline if very ill or dehydrated, and if necessary a blood transfusion.

He is given 50,000 units of penicillin intramuscularly every three hours for ten days or two weeks.

Also he received sulphadiazine 0.2-0.25 gm./kg. body weight in 24 hours. The drug is given every four hours with 0.6-1.0 gm. sodium bicarbonate.

The extremity is not immobilized.

If a soft tissue abscess forms nothing is done unless it seems likely to rupture in which case the pus is aspirated through healthy skin.

With this method of treatment these patients do very well indeed. The temperature falls to normal and the local signs and symptoms subside rapidly.

Sequestrectomy, which is seldom necessary, is performed when the sequestra have separated, not often before six months. Small sequestra will become revascularized; large loose ones will not and should be removed. In the chronic stage of the disease the antibiotics are very useful but I have no thought that they are a substitute for an adequate operation.

It is felt that children with acute hematogenous osteomyelitis die of an overwhelming septicemia. They do not die because one neglects to drain an abscess in bone.

I believe firmly that operation in the acute stage does nothing but harm. It does not seem to me that early operation (and I have done many in the past), in any way lessens the amount of bone destruction and certainly it often resulted in persistent sinuses which contain mixed bacteria. I repeat, early and adequate treatment with penicillin and sulphadiazine aborts the disease with minimal bone change and lowers the mortality almost to zero.

We have been using penicillin as a routine measure in osteomyelitis only since January 1945. From January 1945 to December 1947 there have been 50 cases, 18 with positive blood cultures. Three have required sequestrectomy. Their wounds healed by first intention. One suffered a pathologic fracture of the femur which has united. There were no deaths and, so far as I know, none of these patients has a sinus.

Enthusiasm in surgery is best tempered by years of experience. I am enthusiastic about the immediate results of osteomyelitis in children, about the late results it is much too soon to speak.

Only last week in Toronto a 91-year-old woman was operated upon who had had osteomyelitis of the femur at the age of 11 with no further trouble until now—an 80 year follow up.

In the past recurrences and relapses have been common. Tsteomyelitis like tuberculosis is arrested not cured. I always remember Professor Gallie's statement that he is now treating patients with osteomyelitis at the General Hospital whom he had cured 20 years ago at the Sick Children's, but the future looks hopeful. Certainly early flare-ups are far less common than they used to be.

In conclusion may I make four observations on this method of treatment.

1. The clinical course of these patients is better than it used to be.
2. There has been less death of bone.
3. Involvement of more than one bone is rare.
4. The mortality in our hospital has been reduced from 20.7% to 3.9%. In the last 50 consecutive cases there has been no mortality.

Round Table Discussion

THE RH FACTOR: PRACTICAL ASPECTS

WOLF W. ZUELZER, M.D., *Chairman, Detroit, Mich.*, WARREN E. WHEELER, M.D., *Columbus, Ohio,* AND MARTHA F. LEONARD, M.D., *Highland Park, N.Y.*

Chairman Zuelzer: Anemia happens to be one of the manifestations of erythroblastosis, but we intend to keep the purely hematologic aspects to a minimum and shall consider the disease as a whole, paying particular attention to its clinical features. The Rh factor which appears in the title of this discussion is likewise only of incidental interest to us. In recent years we have heard too much about Rh and too little about the clinical entity erythroblastosis fetalis which is our topic for today.

We have agreed for our purpose to define erythroblastosis as a disorder of fetal and neonatal life resulting from maternal sensitization against antigens of the Rh group present in the fetal cells. We exclude deliberately the still controversial cases of so-called erythroblastosis due to incompatibility in the O-A-B system of blood groups and will touch on this problem only in so far as it has a bearing on diagnosis.

Only a few words are needed in regard to the Rh antigens. The emphasis on the subtypes of Rh which are of interest mainly to the geneticist and immunologist have made the subject unpalatable to the clinician and the unnecessarily complex nomenclature has further beclouded a basically simple issue. For the clinician the original Rh antigen with a distribution of 85% in the white population is still by far the most important. In the simple language of the Fisher-Race theory we are chiefly concerned with the genes D and d, familiar to some of you as Rh_o and rh. The genetic background of maternal isoimmunization can be summarized by the simple statement that sensitization is possible only when a homozypous mother carries a heterozygous fetus. An heterozybous mother (Dd) cannot be sensitied since both antigens are present in her own cells. The homozygous fetus (DD or dd) cannot sensitize its mother because by definition it receives the same type of gene from both parents and must therefore be compatible with the mother. In the usual situation of erythroblastosis the mother is Rh negative (dd), i.e. homozygous, the Rh positive fetus is ipso facto heterozygous (Dd). Rarely a homozygous Rh positive mother may become sensitized to the c-d-e genes of a heterozygous fetus.

While the basic relationship of erythroblastosis fetalis to antigenic differences between mother and fetus is well established it seems only fair to say that we know as yet very little about the reasons why certain women become sensitized and others not. We are also ignorant of the actual mechanism by which maternal sensitization produces disease in the offspring. The various theories regarding this question could be passed over completely in a discussion of practical aspects if they did not affect the management of erythroblastosis. The currently prevailing school of thought holds that hemolytic anemia is the essence of the disease and that all its manifestations directly or indirectly stem from a primary process of destruction of Rh positive red corpuscles. Consequently all the attention is directed toward prevention or treatment of the anemia. This view is based largely on negative evidence, namely on the failure of most authors to demonstrate Rh antigen in tissue cells other than red corpuscles. On clinical and pathologic grounds the concept seems unsatisfactory. It does not establish satisfactorily the mechanisms responsible for the development of edema, of kernicterus, of organic damage to the liver, of hypertrophy in the islands of Langerhans as sometimes seen at autopsy. For these reasons we reject the term congenital hemolytic disease as one-sided and prefer to retain the name erythroblastosis which, though inadequate, has at least the merit of historic tradition.

Our own working hypothesis has been that the primary damage in this condition is not limited to the red corpuscles but involves in some direct manner the tissues themselves. This view has some support from Boorman and Dodd's as yet unconfirmed demonstration of Rh antigen in various tissues and from Witebsky's more recent studies showing Rh antigen in the amniotic fluid. To me at least it seems likely that something like an antigen-antibody reaction takes place in the tissue cells of various

* From the Annual Meeting of the Academy, Dallas, Tex., December 8-11, 1947.

organs. This working hypothesis has the advantage that it directs our attention once more to the patient as a sick newborn rather than as a mere receptacle of antigens and antibodies in the blood which can be titrated, added or withdrawn at will.

Our purpose today is the presentation of data which have bearing on the natural history of erythroblastosis, its clinical variants, its prognosis under controlled conditions, its complications and sequelae. We hope that such an analysis can contribute to a clinical evaluation of the various forms of therapy proposed thus far chiefly on theoretic rather than empiric grounds. Some of these procedures, therapeutic and prophylactic, have already found widespread application before they could be adequately tested. It is likely that harm has been done as the result of dogmatic statements or of a desire to "do something," sometimes instilled by public pressure following prematurely released claims. Regardless of its logic no procedure should be accepted without proof. Such proof must in the end be clinical and must take into account the tremendous maternal variability of the disease. This fact has been neglected by most of the proponents of one or the other measure who have tried instead to substantiate their claims by so-called illustrative cases. Such an approach is unsound in a condition which may be naturally so mild that the diagnosis must be made in the laboratory and no therapy at all may be required or, on the other hand may prove fatal in spite of drastic treatment. Because of the difficulties experienced by all of us in predicting the course of the individual patient only the painstaking analysis of a large and well controlled case material can prove the efficacy of any therapy in this disease. The lack of such studies is making itself felt in the development of flatly contradictory ideas and practices and the result has been a loss of confidence and a state of confusion. The practicing physician is asked to make his choice between a variety of magic formulas on faith and without the background of facts to which he is entitled. Moreover, he is often left with the impression that these magic formulas can substitute for clinical observation and judgement, relieving him of the need to individualipe the care of his patients.

In this situation it seemed desirable to go back to first principles and we have conceived our task largely as one of basic orientation. We have no special therapy to defend and no cure-all to offer. We hope to keep our minds open to the merits of any procedure so long as it can be shown to work.

The stage for a clinical re-appraisal of erythroblastosis has been set by the recent advances in the immunology of the Rh antigens which have provided us with new and exact diagnostic criteria. It is now possible to recognize cases which formerly could not be diagnosed and conversely to exclude conditions which in the past were indistinguishable from this entity. Clearly the picture of the disease has been influenced by these improvements in diagnosis.

We shall first discuss the means of diagnosis. Subsequently we shall attempt to examine specifically the evidence for certain assumptions regarding the course and prognosis in erythroblastosis on which therapeutic claims are often based.

1. How can we judge the severity of a given case? What correlation exists between each of the common symptoms and the immediate outlook? Whate significance can be attached to the various laboratory findings such as the degree of anemia, the number of circulating nucleated red corpuscles, the icterus index, etc.? How can we evaluate the presence of maternal antibodies prior to birth and what relation does the type and titer of these family history have? How many exceptions are there to the rule that the progresses in severity from one child to the next?

2. Is the outlook in prematurely born infants better than in full term infants with erythroblastosis?

3. What are the preventable complications of the disease? What is the nature and the incidence of nonpreventable complications which would produce a residual mortality even if the disease proper and its preventable complications could be controlled?

4. What is the overall mortality of erythroblastosis under a given set of conditions where therapy is kept constant and no arbitrary selection of cases is made?

5. What late sequelae of neurologic character can be expected and what correlation exists between these and the initial symptoms of the disease?

In examining these questions we are well aware that the answers will be influenced by the particular case material which happened to be available to us. For this reason each of us will take part in examining these points so as to give as representative a picture as possible. Even so we expect our experience to differ from that of others working with different material. However, the cases which are seen by Dr. Leonard in New York, Dr. Wheeler in Columbus and myself in Detroit are probably fairly typical of the patient seen by the average pediatrician. In order to make our data significant,

rigid criteria were applied to our material and all cases which did not meet these criteria were excluded from the series even though they might have been very obvious examples of erythroblastosis. The criteria agreed on by our group were:

1. Clinical manifestations of erythroblastosis in the patient.
2. The demonstration of antigenic differences between fetus and mother.
3. The successful demonstration of maternal antibodies during the neonatal period.

The analysis will be concluded by Dr. Wheeler's discussion of therapy.

Dr. Leonard: The clinical picture in erythroblastosis is a varied one. On the basis of the outstanding manifestation, cases were formerly diagnosed as hydrops fetalis, icterus gravis neonatorum, or congenital anemia—each considered a seperate entity. We now know that these symptoms of edema, jaundice, and anemia to be part of the picture of erythroblastosis, varying independently in different patients. A typical, moderately ill patient is jaundiced at birth or becomes jaundiced within the first few hours. The amniotic fluid may be yellow. He may be slightly listless or have puffiness of face or feet. Even at birth a definite pallor may be evident beneath the jaundice, or this may become apparent during the first week or two. Examination of the infant reveals a firm enlargement of liver and spleen, extending 1 to 4 cm. beneath the costal margin. The characteristic blood picture is one of moderate anemia with increased numbers of normoblasts, erythroblasts, and often immature leucocytes. Icterus index and vanden Bergh reaction (predominantly indirect) are elevated. The urin contains bile. Prothrombin time is frequently prolonged.

My remarks are based on study of 47 infants with erythroblastosis, treated in the Pediatric Department of the New York Hospital between 1941 and 1947. Six of these cases were included in a series previously reported from the New York Hospital, but the rest of that series were excluded because tests for immunization had not been done. Forty-five were white and two were Negroes.

The clinical feature most commonly noted was jaundice, present in 40 of the patients. It was noted at birth in 10 infants and developed within 24 hours after birth in an additional 17 patients. Usually it persisted from 1-3 weeks, but one child remained icteric for 50 days. Twenty infants were deeply icteric or had an icterus index more than 100. In 11 infants the amniotic fluid was yellow.

Liver or spleen or both were enlarged in 40 infants. Fourteen patients had marked splenic enlargement, 15 slight and 17 no demonstrable splenomegaly. Hepatic enlargement was absent in 12 patients, present in 33, and marked in 25 of these.

Edema was noted in 15 patients and was pronounced in 10 of these. Other frequent signs of illness were cyanosis, listlessness, a weak or high-pitched cry, twitching, a poor sucking reflex and vomiting. These findings seemed to us of poor prognostic import.

Many infants were not anemic at birth but with only two exceptions all developed some degree of anemia while under observation. The initial hemoglobin levels ranged from 1.5 to 20.5 gm. Of the patients seen during the first 24 hours of life only three had hemoglobin levels below 9 gm. The lowest hemoglobin value for each patient ranged from 1.5 to 13.4 gm. and was reached in a few instances as late as four months after birth. Correction of the anemia required from 40 to 1245 cc. of whole blood given from the date of birth through a period as long as 99 days. No correlation was found between the degree of anemia and that of jaundice. Icterus index and hemoglobin level fluctuated in the same patient. Jaundice often decreased while falling hemoglobin levels indicated continuing hemolysis.

The nucleated red cell counts varied from 0 to 1500 per 100 leukocytes. These cells persisted as late as 53 days but usually their number decreased rapidly after the first few days of life. Thirty-three patients were never found to have a nucleated red cell count of more than 100 while 14 had counts ranging from 100 to 1500. No correlation was found between the degree of erythroblastemia and the severity of the anemia or the type of maternal antibody. Marked enlargement of the spleen was almost invariably associated with a high nucleated cell count in the circulating blood.

The criteria for clinical diagnosis are therefore jaundice, anemia, edema, hepatosplenomegaly and erythroblastemia. The variability of these signs and symptoms, however, makes diagnosis on clinical grounds alone somewhat difficult, particularly in mild cases. Usually two or more of these findings are present, but any one may be absent. Each manifestation may vary independently of the others.

Chairman Zuelzer: The diagnosis of erythroblastosis often can be suspected because of the family history, even before the patient is born. A typical family history with multiple instances is almost unmistakable but a word of warning is in order regarding the prenatal diagnosis from the history of the preceding births. In the case of a heterozygous father the infant may prove to be Rh negative and normal. Secondly, still births, miscarriages and cases of jaundice and anemia in the new born do occur from causes other than erythroblastosis. It is dangerous to jump to conclusions. An Rh negative mother may just as readily lose a child from other causes as the Rh positive woman. A history of abortion alone in an Rh negative woman is no basis for the diagnosis of sensitization, yet I know of a number of instances where women were warned against further pregnancies on such inadequate evidence.

The prenatal diagnosis must at least be substantiated by the determination of antibodies in the

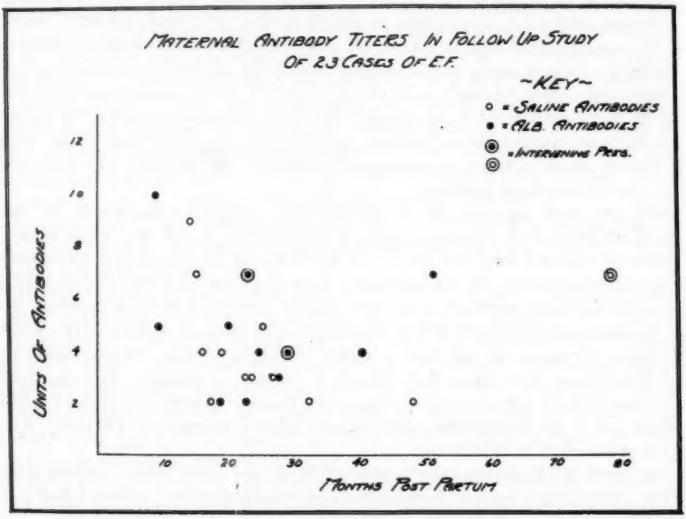

FIG. 1

mother's serum but even this promising tool has definite limitations. Of 68 multiparous Rh negative women with Rh positive husbands recently referred to our laboratory during the last trimester of their pregnancy, 12 had anti-Rh antibodies in their serum. Erythroblastosis developed in the offspring of 10 of these women. The remaining two mothers gave birth to children in whom even the most careful clinical observation and laboratory study failed to show any signs of disease. One of these infants was Rh negative, the other, even more remarkably, was Rh positive. Both mothers had previously given birth to infants with erythroblastosis. In such women the presence of antibodies is therefore not necessarily indicative of renewed sensitization but may merely mean a carry over from the preceding pregnancy. This is supported by data in Figure 1 showing the persistence of antibody in the mother's serum as late as 52 months postpartum. None of the 23 women tested in this study failed to show antibodies.

Even a rising titer of antibody in the course of pregnancy is not conclusive. This phenomenon was observed in the woman who subsequently gave birth to an Rh negative, healthy infant and Dr. Wheeler has had three similar experiences. We can only assume that such rising titers following an earlier, sensitizing pregnancy indicate the occurrence of non-specific anamnestic reactions. Where there is no history of erythroblastosis, the finding of antibodies in the mother's serum is much more significant. Thus far I have seen no exception to the development of clinical erythroblastosis in the offspring of such women. To sum up, given a history of erythroblastosis in preceding children, the finding of maternal antibodies during gestation, even with rising titers is not

conclusive evidence that the infant will be affected. Without such a history, mere presence of antibodies in the mother's serum almost certainly indicates erythroblastosis. In the absence of antibodies in the last 2-3 months of gestation erythroblastosis can be confidently ruled out. Of 75 Rh negative women whose serum did not contain antibodies during the last trimester 72 delivered normal infants. Two had still births, one as the result of chronic nephritis with hypertension and an extensively infarcted and necrotic placenta, the other from strangulation due to twisting of the umbilical cord. In both cases autopsies were performed which failed to show any of the common findings of erythroblastosis. One woman, a primigravida, gave birth to a living child who developed an unexplained anemia during the newborn period but recovered spontaneously. In these last three cases the histories alone might be misleading, but of course lack of sensitization against Rh does not guarantee freedom from other hazards of fetal and neonatal life.

It is clear that prenatal serologic studies are of great value in determining the probability of erythroblastosis but positive diagnosis should not be made on such grounds at the present time.

The practice current among some obstetricians of terminating pregnancy by abortion or prematurely induced labor because of rising antibody titers during pregnancy seems hardly justified. To emphasize this point I shall briefly give a case history: Mrs. M., an Rh negative woman had previously lost a baby shortly after birth with typical symtoms of erythroblastosis. She presented herself 18 months later in the second month of her next pregnancy. Her husband was tested and found to be Rh positive, presumably heterozygous. Mrs. M.'s serum contained antibodies of a titer of 1:2 in albumin. The titer was followed at monthly intervals and remained stationary until the sixth month when it rose sharply reading 1:1024 at seven months. At eight months a cesarean section and sterilization by tubal ligation was performed. The infant weighed 2500 gm. at birth and appeared normal except for marked respiratory inertia. Blood studies showed normal hemoglobin values. The infant proved to be Rh negative. Although free antibody was present in his serum, appropriate tests showed that no coating of the red cells with antibody had occurred. Three days later the baby died with respiratory failure. He had not become jaundiced or anemic and at autopsy the only abnormal finding was pulmonary atelectasis. The conclusions to be drawn from this case are only too obvious. We shall be on safer grounds with the serologic diagnosis of Erythroblastosis in the newborn which Dr. Wheeler will now discuss.

Dr. Wheeler: Since it was demonstrated several years ago that all mothers of erythroblastotic infants show the blocking type of antibody in their serum, a serologic diagnosis of erythroblastosis has depended upon the demonstration of such antibodies in the mother's serum plus the demonstration that the baby is Rh positive. More and more exceptions to these two criteria are becoming apparent. Instances have been noted in which Rh positive babies have been erroneously typed Rh negative because their cells were "blocked." We, also, have seen two instances in which the mother developed a low titer of antibodies late in the course of her pregnancy and whose baby showed no clinical features of erythroblastosis, although the baby was Rh positive. If the disease process in the baby is dependent upon an antigen-antibody reaction, then the precise serologic diagnosis should depend upon the demonstration of an antigen-antibody combination in the baby. This can be done by demonstrating the presence of red cells in the baby which have been sensitized by specific anti-body. The sensitized red cell is one which is coated with anti-Rh anti-body of the so-called blocking type. This coating has a rather firm attachment in some respects, and it is the coated red cell which distinguishes a baby with erythroblastosis from any other baby. Because of the nature of the blocking antibody, these sensitized red cells do not agglutinate, and intravascular agglutination does not seem to be a feature of erythroblastosis. If we had at our disposal a laboratory method for accurately differentiating the sensitized red cell from the unsensitized red cell, we would, therefore, have a method for diagnosing erythroblastosis using the baby's cells alone whether or not the mother's serum was available for testing. This can be done in a number of ways as we now know.

In the first place, the antibody globulin coating on the cells can be specifically precipitated by means of appropriately absorbed rabbit serum which contains antibodies against human globulin. This reaction causes a visible clumping of the sensitized cells similar to agglutination. The test was first described by Coombs and has been referred to as the developing test or the anti-globulin test. This reaction is very sensitive and will demonstrate sensitized cells present in the baby's circulation in certain cases as long as seven weeks after birth. The test has one great failing in that sufficiently potent anti-human antibodies are difficult to develop in a rabbit, and the reagent is not

commercially available. The sera we have worked with have shown a strong tendency to deteriorate. Using this test on our patients, we have successfully demonstrated sensitized cells in eight cases.

Another property of the sensitized cell is its ability under suitable conditions to give up the antibody which is attached to the cell surface. The cells of a baby with erythroblastosis are washed free of serum antibodies and are then resuspended in a solution of albumin or glue and are heated at 50 degrees for 30 minutes. While still warm the supernatant solution is removed, and it can be demonstrated to contain anti-Rh antibodies by the clumping of freshly added Rh positive test cells. This test has one advantage over the others proposed for the same purpose in that one can use cells containing single Rh antigens (Rh_0, Rh', Rh'' = C, D, E) for the test cells and determine the exact specificity of the antibody which is combined with the baby's cells. The technic is not as delicate as the Coombs' test and has failed us on three occasions when our babies had first been seen at more than a week of age. In other words, this test must be used early in the course of the disease for uniform success. We have been successful in demonstrating released antibody in 24 cases where albumin has been used as a suspending medium and in eleven cases when the glue solution has been used. In six instances the test was positive in both media.

The use of albumin or glue solution as a suspending medium is the basis for the so-called "conglutination" phenomenon of Wiener, and its usefulness depends on the fact that sensitized cells

FIG. 2. Contact Print of Glue Test for Sensitized Cells (allowed to dry)

Both tests are from 48 hour old Rh positive jaundiced babies of Rh negative mothers. The left hand drop represents cells of a baby affected by erythroblastosis due to maternal anti-Rh antibodies. The right hand drop represents unagglutinated cells of a baby affected by *icterus precox* presumably due to the high anti-A antibody titer of the maternal serum.

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suspended in these media will visibly clump together. Several technics of demonstrating sensitized cells have been based on this phenomenon, and we have had some success showing agglutination of washed red cells when suspended in albumin, plasma, whole Rh positive blood, and glue solution. All of these techniques, when carried out in test tubes, were found to be wanting in certain instances. However, when a drop of whole oxalated blood from a baby with erythroblastosis is placed on a slide and a drop of glue solution (LePage's glue (#10) 1 part, and normal saline 6 parts) is mixed with the whole blood by means of a toothpick in the manner of the Diamond open slide test, sensitization of cells is immediately evident by gross clumping of the cells. This reaction takes place usually within one minute and is very striking (Figure 2). A report by Witebsky proposes the same sort of a test done on a slide using pooled human plasma instead of glue, and he claims his test is quite specific and does not give false reactions. I am sure that his test is practically the same as ours. In our hands we have had 15 cases of erythroblastosis so far which have shown a positive test, and it has failed us only once, in a patient who was 20 days old. This is a procedure in the process of development. Dr. Zuelzer has repeated these findings on his material, and he tells me that he has had a little trouble with rouleaux formation on the control part of the test (whole oxalated blood from a normal individual mixed with a drop of glue). The test should always be carefully controlled by the use of a similar drop of whole blood from a patient known not to have sensitized cells since slight degrees of rouleaux occasionally are seen.

The usefulness of procedures such as these is illustrated by the following two cases. In the first instance a 12 hour old baby was admitted to the hospital from a distant town with a history of developing irregular respirations and cyanosis at the age of two hours. On admission the baby's face was puffy, he showed a large number of petechiae, and he was bleeding from several orifices. He had a large liver and spleen, 5.5 gm. of hemoglobin, 177 nucleated red cells per 100 white cells,

and a prothrombin of 10%. He was not jaundiced; however, he was only 12 hours old. Clinically it appeared as though he might have erythroblastosis. A test of the baby's cells showed them not to be sensitized, and the baby was, therefore, treated with transfusions and antibiotics as a case of sepsis. A day later when the mother's blood became available, it was found that she was Rh positive and had no abnormal antibodies against the baby's cells. Despite the treatment, the child died at 48 hours and autopsy revealed evidence of a sepsis which had probably been present in utero, and in addition renal cortical necrosis. In this instance the test for sensitized cells helped us eliminate erythroblastosis as a possible diagnosis and focus our attention on the real nature of the disorder.

TABLE I

COMPARISON OF "CONTROL" GROUP WITH ERYTHROBLASTOSIS GROUP

No. of Cases	Control	Percent	Erythroblastosis Fetalis	Percent
Rh positive mothers	45	(77.5)	1	(01.0)
Rh negative mothers	11	(19.0)	97	(99.0)
Mother's Rh type unknown	2	(03.5)	0	
Total	58		98	
Compatible with mother in O-A-B system	28	(48)	91	(93)
Incompatible	29	(50)	7	(07)
Unknown	1	(02)	0	
Total	58		98	
Race: White	42	(72.4)	107	(100)
Negro	16	(27.6)	0	
Total	58		107	
Prematurity	18	(31)	10	(09)
Full term	40	(69)	87	(82)
Birth weight unknown	0		10	(09)
Total	58		107	

Another baby was seen at the age of 18 hours of age because of irregular respirations. The baby was slightly jaundiced at that time, and the father stated that the mother's first pregnancy had resulted in a stillbirth which at autopsy had proved to be due to erythroblastosis. However, blood tests on the father and mother at another hospital at that time had shown them both to be Rh negative. The baby showed no other features of erythroblastosis, but on a long chance blood was obtained from the mother, baby, and father. All the bloods tested the next day showed the reaction of Rh_o', (CDe). However, the baby's cells were sensitized, and the mother's serum contained antibodies against Rh_o cells. It was then found that our typing sera had become contaminated, and the true type of the mother was Rh′ (Cde), the baby Rh_o (cDe), and the father Rh_o' (CDe). The baby was, therefore, considered an erythroblastotic infant, and over a period of three and a half weeks the hemoglobin fell to 9 gm. Jaundice persisted about a week. Three transfusions were given at three and a half, five, and six and a half weeks following which the baby proceeded to make his own red cells, and since then he has done well. This instance is one of the mildest cases of erythroblastosis of which we are aware. The true nature of the disease was proved by the presence of sensitized cells in spite of the comedy of errors concerning the types of the members of the family.

Chairman Zuelzer: Dr. Wheeler's remarks call for one comment, namely that he is a careful worker and a first-rate immunologist. The "glue test" which he has described works in his hands and has worked well in our laboratory in the few cases in which we have had the opportunity to use it. I only wonder if the time is ripe to turn this technic over to the average laboratory technician. We must realize that many physicians depend on reports from laboratories which are not qualified to perform or interpret these delicate tests, yet far-reaching decisions may be made on the basis of such reports. Those of us who know the pitfalls in the technics of Rh work realize that the tests are only as reliable as the hands which carry them out. There is no question, however, that a simple, rapid and accurate method for the demonstration of sensitized red cells would mean a tremendous step forward.

Our next problem is that of the differential diagnosis. To illustrate this problem I have selected from our case material all those patients in whom the diagnosis of erythroblastosis was suspected

TABLE II

DIAGNOSIS IN 58 CASES OF SUSPECTED ERYTHROBLASTOSIS FETALIS IN WHICH RH SENSITIZATION WAS RULED OUT

Reason for Rh Studies	No.	Eventual Diagnosis	No.
Icterus	30	Prematurity	8
		Normal infant	7
Suggestive family history	7	Sepsis	6
		Physiologic icterus	5
		Birth injury	5
Bleeding	6	"O-A incompatible"	4
		"Hepatitis"	4
Kernicterus at autopsy	6	Intestinal obstruction	4
		Asphyxia	4
		Diarrhea of newborn	3
Anemia	4	Hemorrhagic disease	3
		Anemia, cause undetermined	2
Other	5	Acute gastric ulcer	1
		Miscellaneous	2
Total	58		58

for some reason but was eventually discarded. This group of 58 cases I shall call the control group. Comparison of this control group with that of infants with erythroblastosis shows first of all the expected predominance of Rh positive mothers. Secondly, we find a surprisingly high number of instances of incompatibility in the O-A-B system in the control group, and the reverse in the erythroblastosis group. It was this latter finding which gave rise to Wiener's theory of the competition of antigens. Thirdly, we find a substantial number of Negroes in the control group. It so happened that all our patients with proved erythroblastosis up the time of this compilation were white infants but of course the disease does occur in the Negro. We note a high incidence of prematurity in the control group—to be expected because the early onset of icterus in these patients was the feature which led to Rh studies—but also a rather high incidence of premature infants in the erythroblastosis group. Lastly the control group includes a larger number of first born infants. Table II shows on one side the symptoms in the control group which led to investigation of possible Rh incompatibility, on the other the eventual diagnosis made. Icterus was the main reason for suspecting erythroblastosis. In six cases the unexpected postmortem finding of kernicterus led to serologic investigation of the family, but erythroblastosis could not be proven in any of the six cases. In seven cases the fact that the mother was Rh negative or had a history of stillbirth was the indication for the study.

The final diagnosis was not always satisfactory. A number of infants seemed normal in every respect. Eight patients showed nothing beyond the signs of prematurity. Five were classified as having physiologic icterus. Four were considered to show effects of O-A incompatibility and we shall have to say more concerning this question. Four were classified as hepatitis, etiology undetermined. These patients continued to have severe icterus and hepatomegaly for a long time and in some instances autopsy demonstrated severe organic liver damage. Six patients had septicemia reminding us of the well known differential diagnosis between icterus gravis, sepsis and syphilis. Birth injury, asphyxia neonatorum, intestinal obstruction and hemorrhage were the other major groups. It may be worth stressing again that with all these conditions the question of erythroblastosis did arise in the mind of the referring or admitting physician seriously enough so that serologic and hematologic studies were requested. Thus with the diagnostic criteria the differential diagnosis has also changed.

Most of the conditions named are readily distinguished from erythroblastosis even on clinical grounds. Two groups of patients, however, had conditions simulating the effects of Rh sensitization rather closely. One consisted of three patients in whom anemia at birth was the dominant symptom. In all three cases some degree of icterus, hepatosplenomegaly and normoblastemia was present. In

TABLE III

MATERNAL-FETAL O-A-B RELATIONSHIP IN ALL CONTROL CASES WITH ICTERUS IN FIRST 24 HOURS

Pt.	Race	No. Preg.	Maturity	Mother's Type	Baby's Type	Titer	Symptoms	Diagnosis
Ant.	W	5	Prem.	A Rh neg.	A Rh_1	0	Icterus at 3 hrs., edema, Petechiae, family history	Atresia of ileum
Bod.	W	7	F.T.	O Rh_1	A Rh_1	256	Icterus 1 day, anemia	"O-A" incompatible
Bos.	N	2	F.T.	O Rh neg.	A Rh_1	2048	Icterus at birth, anemia	"O-A" incompatible
By.	N	1	F.T.	O Rh neg.	A Rh neg.	128	Icterus at birth, lethargy	Birth injury
Car.	W	2	F.T.	O Rh neg.	A Rh pos.	256	Icterus at 1 day	Physiological icterus
For.	W	1	F.T.	O Rh neg.	A Rh,	4096	Icterus at 1 day, later anemia	Physiological icterus
Kuc.	W	6	Prem.	O Rh_1	A Rh pos.	256	Icterus at 1 day	Cerebral hemorrhage
Ste.	W	1	F.T.	O Rh_1	A Rh_1	512	Icterus 1 day, anemia	O-A incompatible
Toc.	W	4	F.T.	O Rh_1	A Rh_1	8198	Icterus at birth	O-A incompatible
Vig.	W	3	F.T.	O Rh_1	A Rh_{1-2}	4096	Family history, icterus at birth, anemia	O-A incompatible
Wil.	N	5	F.T.	O Rh_1	B Rh_1	4096	Icterus at birth, large liver, later anemia	"Hepatitis"

one case there was a history of neonatal jaundice and anemia in three preceding siblings, two of whom had died. The diagnosis of erythroblastosis was at first made in spite of lack of antibodies in mother or infant and in spite of compatible Rh and O-A-B types. It had to be abandoned however, when both the surviving sibling and the patient continued to show evidence of active, severe hemolytic anemia over a period of months and years. The nature of this familial and congenital hemolytic anemia is at present obscure—erythrocyte fragility was normal and the parent's blood showed no abnormalities— but this example shows that not every neonatal anemia with jaundice is necessarily erythroblastosis. The second case in this group was almost identical with the one just mentioned but this patient was the only child so that the familial incidence could not be established. The anemia responded to splenectomy at ten months. The third case was that of a Negro infant who died on the first day of life. Mother and child belonged to the same blood and Rh groups and antibodies were absent in either's serum. Autopsy findings failed to throw light on the nature of this mysterious case which could easily have passed for erythroblastosis.

The second diagnostic problem was presented by those patients who exhibited icterus at birth or in the first 24 hours in the absence of Rh incompatibility. Table III illustrates the striking fact that of the ten unselected patients in this group nine were incompatible with their mothers in regard to the O-A-B blood groups. In none of the ten cases could maternal antibodies against Rh be shown. The maternal anti-A or anti-B titers were only moderately high or in the range considered high

normal for our technic. Testing against albumin-suspended cells did not yield higher titers. Most of the patients subsequently also had some degree of anemia. In two instances a family suggestive of neonatal icterus in preceding siblings was obtained. Survival was the rule except where other conditions fatal in themselves were present.

This is the group to whom Wiener refers as icterus praecox and others as O-A-B erythroblastosis. Whether or not there is such an entity, these are the patients who present the most difficult diagnostic problem. The differentiation from erythroblastosis may be suggested by the O-A-B incompatibility which, as you saw, is rather rare in true Rh sensitization disease, by identity of Rh types of mother and child, sometimes by the fact that the patient is the first born in the family. Because these patients usually do well without treatment or at most with routine transfusions the separation of such cases from true erythroblastosis is important and, in the last analysis must rest on careful serologic studies. Dr. Wheeler's glue test would be particularly valuable here.

One of the main problems facing the clinician in erythroblastosis is the evaluation of the severity of the disease. Everyone with experience in this field is aware of the difficulties in sizing up these patients when they are first seen. Yet not only the prognosis but the rational treatment depend greatly on one's ability to predict the course of the illness in a given patient. Dr. Leonard will begin our analysis of the significance of clinical and laboratory findings which have been utilized for this purpose.

TABLE IV

CORRELATION OF SEVERITY AND THE TIME OF APPEARANCE OF JAUNDICE WITH TYPE OF ANTIBODY

	Severity of Jaundice			Time of Onset		
	Absent	Mild	Severe	Birth	1st Day	After 1st Day
Blocking antibody	2	11	8	7	7	5
Agglutinating antibody	2	3	5	1	4	3
Both	1	2	0	0	1	1
Total	5	16	13	8	12	9
Fatal cases	2	3	3	2	4	0

Dr. Leonard: Of our 47 patients 34 were born in the Lying-In Division of the New York Hospital and most of these were transferred immediately or within a day or two to our Pediatric Department. A few were transferred later and a few had been sent home as normal infants only to be readmitted at 3-4 weeks of age because of progressive anemia. The other 13 infants were referred by other hospitals or practicing pediatricians and with one exception had been well treated and well observed. The usual reason for admission in this group was anemia. The exception was a child who had been dropped on its head during a home delivery and whose course was stormy and ended in death. The treatment of the patients was fairly uniform during the period covered by this survey. The feeding routine was standard. In addition to formula each infant received supplements of vitamin A, B, C, D and K and many patients also were given liver extract. Except for one child who died too soon, all patients were treated by transfusion. The blood given nine of these patients was not typed for Rh. Three infants were deliberately given Rh positive blood. The remainder received Rh negative blood, usually by multiple small transfusions except for the last six patients who were treated by the exchange transfusion method.

In our group the severity of jaundice seemed of little prognostic importance. The same proportion of fatalities occurred in patients with mild as in those with severe jaundice. The time of onset of icterus seemed more significant. Of 27 patients showing this symptom at birth or within 24 hours seven subsequently died. In the group of 13 infants who became jaundiced after the first day only one fatality occurred.

We also attempted to correlate the presence and severity of the icterus with the type of maternal antibody but the table shows that in this small group there was no such correlation (Table IV),

Severe edema was a sign of serious prognostic importance. Of the 15 infants with edema, the five patients with the most marked degree, corresponding to the type known as hydrops all died. Respiratory disturbances, neurologic signs were also more often noted in the fatal cases than in the survivors.

The degree of anemia was not in itself an index of the severity of the disease. The infants with very low hemoglobin levels were usually those admitted late in the course of the disease. There were only three infants who had initial hemoglobin levels of less than 9 gm. Two of these died suggesting that severe anemia at birth indicates a serious prognosis. After the first few days the degree of anemia seemed to make little difference in the outcome. Table V shows an attempt to correlate the degree of anemia with the type of maternal antibody. The range of initial hemoglobin levels was almost the same whether the mother's serum contained blocking or agglutinating antibodies. The lowest level reached by each patient in the two groups is also similar, simply because that level was considered an indication for transfusion. We also found a lack of correlation between the titer of the maternal antibody and the degree of anemia in the infant. Mothers with high titers of antibody might have infants with little or no anemia.

There were five deaths among 32 infants with less than 100 nucleated red cells per 100 white cells and five deaths among 14 patients with more than 100 such cells showing a higher death rate in the group with the most marked normoblastemia. We found that prior to last year when we

TABLE V

CORRELATION OF ANEMIA WITH TYPE OF ANTIBODY

	Initial Hemoglobin (gm.)	
	Range	Mean
Blocking antibody	5.0–20.5	11.8
Agglutinating antibody	4.0–18.0	17.0
Both	7.2–11.5	10.0

began to use exchange transfusions, of patients with a nucleated red cell count of more than 200/100 leukocytes only one had even survived and only two more had lived among the group with more than 150 nucleated cells. Dr. Zuelzer's material is similar in this respect showing that a high absolute count of nucleated red cells is a bad prognostic sign.

Chairman Zuelzer: The data just presented suggest that certain findings such as anemia or icterus at birth, severe edema, marked erythroblastemia, neurologic symptoms and generally poor condition of the infant indicate a grave prognosis. In examining our material I have taken some of these and certain other findings and tried to correlate each single symptom with the outcome. Our material differs from Dr. Leonard's in that the patients were admitted in quite variable conditions. Some were referred immediately after birth or during the first day, others were brought to us after they had been treated elsewhere for a number of days. A goodly number of infants had not been well cared for and were brought to the Children's Hospital because their condition was getting worse. Some were actually moribund on admission. Consequently the outlook in our group is influenced by the admission age and by a high incidence of complications. The total group comprises 107 cases, not all studied in the exactly same manner so that the data are not complete on every point covered by this survey.

The manner of treatment, once the patients were admitted to the hospital was fairly uniform consisting of a standard feeding regime, multiple transfusions, maintaining the hemoglobin level above 10 gm. during the first two weeks of life, and supportive measures as indicated. With few exceptions we used group-specific Rh negative whole blood drawn freshly or preserved in a vacuum bottle. In three instances Rh positive blood was deliberately used without appreciable difference in clinical or hematologic response.

Figure 3 bears out Dr. Leonard's statement that enemia need not be present at birth and is

therefore not an early diagnostic criterion but develops almost invariably during the first two weeks. We may be skeptical of the diagnosis if anemia fails to develop. The graph also shows the high mortality associated with low hemoglobin levels on the first day of life. This then does seem to be a serious prognostic sign. Our material shows also that the patients with early icterus fell into

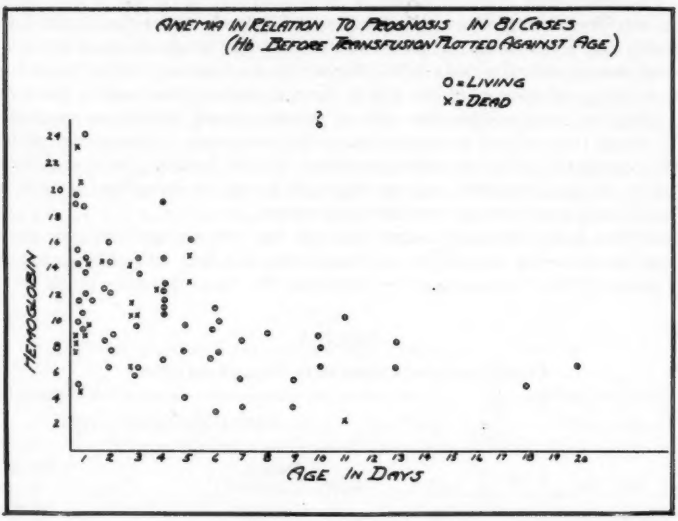
ANEMIA IN RELATION TO PROGNOSIS IN 81 CASES
(Hb BEFORE TRANSFUSION PLOTTED AGAINST AGE)
O = LIVING
X = DEAD
HEMOGLOBIN
AGE IN DAYS

FIG. 3

the group with the highest mortality but given the symptom of icterus at birth alone, one could not predict the outcome. Of 36 patients icteric at birth 21 lived and 15 died. Of 46 infants with icterus developing in the first 48 hours 36 lived and 12 died (Table VI). We cannot say then, that the prognosis is necessarily poor because a baby is icteric at birth. I should like to stress this point as we have already discussed patients who are icteric at birth but who do not have erythroblastosis.

Figures 4 and 5 show the maternal antibody titers in two groups of patients, those who survived and those who died. Both groups show marked scattering over approximately the same range. In our material there is a complete lack of correlation between maternal titer and prognosis for the infant. We have been told that a rising titer during pregnancy indicates a poor prognosis and some obstetricians consider this sufficient grounds for premature delivery by cesarean section or induced

TABLE VI

CORRELATION OF ONSET OF ICTERUS WITH PROGNOSIS

	No. of Cases		
	Surviving	Dead	Total
Icteric at birth	21	15	36
Icteric in first 48 hours	36	12	46
Icteric after 48 hours	13	1	14
Onset of icterus, unknown	1	0	1
Not icteric	4	0	4
Total	75	28	101

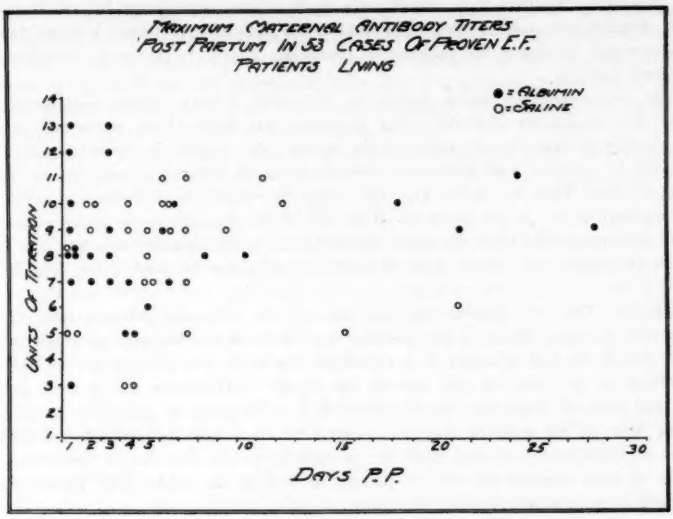

FIG. 4

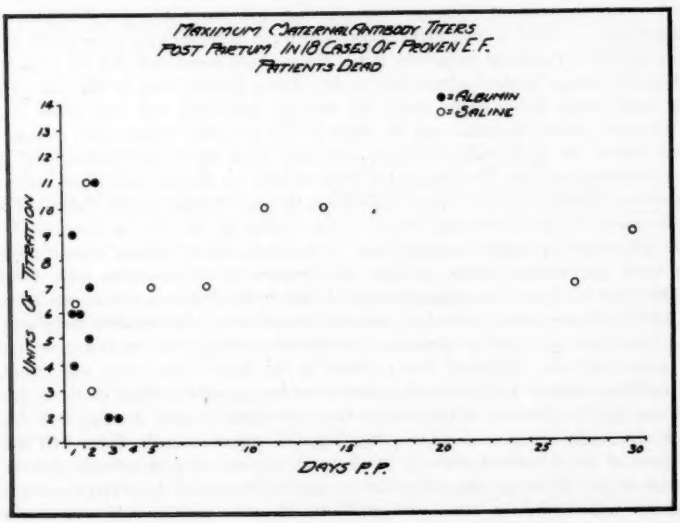

FIG. 5

labor. The substantial number of survivors with high maternal antibody titers in our group of cases must make us skeptical.

That edema in its most severe form, hydrops universalis is a grave sign is a matter of common knowledge. Such cases were not encountered in our material of referred patients. Less marked edema was present in eight infants. Of these four lived and four died. If a patient showed this symptom the chances of survival with standard treatment were still 50%.

Purpura which we expected to be a very serious sign was present in six patients of whom four

survived. Neurologic findings were also thought to be a grave significance but of 22 patients with symptoms ranging from convulsions, opisthotonos and spasticity to severe lethargy bordering on coma, 15 survived. Evidently the presence of neurologic symptoms per se is not a bad prognostic sign as regards survival.

The only single symptom which enabled us to predict a fatal outcome with more than 50% probability was respiratory difficulty. This symptom, has hardly been mentioned in the recent literature, largely perhaps because many of the reports were written by immunologists rather than clinicians. Of 19 patients with respiratory distress, grunting, labored respirations or cyanosis only five lived, 14 died. That was to be expected, since the respiratory difficulty was often related to serious complications but in any event an infant who shows this sign is one about whom we should be gravely concerned. We shall see later whether there is any specific basis for this finding and whether we can expect any specific form of treatment to prevent or combat this difficulty.

Dr. Wheeler: The cases representing our material are somewhat different from those of Dr. Zuelzer or Dr. Leonard. None of our patients were born in our hospital, although half of them reached us within the first two days. It is significant that of the five patients of ours who died, four were admitted on the first day and one on the second. Furthermore, all of these patients were autopsied and none of them were found tohave died of infection or aspiration. In recent months, because we have an Rh antibody diagnostic service which is used by most of the obstetricians in our town, we have been receiving most of our patients on the first day of life. This, of course, means that we have received the severest patients as well as the milder ones which might survive and only come to the hospital after five or six days.

In our case material it has been so difficult to estimate the degree of severity of erythroblastosis even in retrospect that we have come to the conclusion that for purposes of analysis there are only three types of babies which we can consider: (1) those who survive and are normal; (2) those who survive but have clinical evidence of kernicterus; (3) those who die. We have studied this case material with an effort to find those factors which can help size up a baby in the first 24 hours of life and foretell his eventual prognosis. It has already been mentioned that the clinical picture of erythroblastosis changes markedly from day to day. Those patients seen in the first 24 hours have extremely large livers and spleens, rarely are severely jaundiced, and only some of them have anemia, although erythroblastemia may be marked. On the other hand, after passage of several days, most babies are profoundly jaundiced and have large livers and spleens, and are anemic, and the erythroblastemia has diminished. For these reasons the data on which the following discussion is based are confined entirely to those collected in the first 48 hours of life. Table VII portrays the six manifestations of erythroblastosis which, when present in the first 48 hours of life, indicate to us an unfavorable prognostic significance. In the right hand column appear the number of occasions these unfavorable clinical features were present in 24 additional cases for which data covering the first 24 hours are obtainable and in which the babies survived and appeared to be normal. Nearly all the babies who had extremely large livers shortly after birth either died or had kernicterus. The presence of edema, and irregular, grunting, and inefficient respirations were likewise quite significant. Although free antibody in the baby's own serum was found a number of times in those patients who survived, it seemed to be invariably present in those that died, and the same can be said about an initial hemoglobin level under 11 gm. An extremely high erythroblast count also seemed to have an unfavorable prognostic significance. In Table VIII it is seen that while no one of these features taken by itself could be used to prognosticate with any certainty the outcome of an individual case, when taken together they seem to differentiate rather sharply those patients who died from those who survived and were normal. You will note that of the patients who survived none had more than three of these unfavorable features and most of them had only one. But of the patients that died, all showed three or more of these unfavorable features. *It is the multiplicity of unfavorable clinical features which carries the unfavorable prognosis rather than any single feature taken by itself.*

Chairman Zuelzer: The assumption is often made that prognosis can be judged by the family history. The implication is that therapy can be credited when a patient survives whose siblings had been affected by or died from erythroblastosis. Let us look at the family histories of these patients.

Dr. Leonard: In view of the widespread acceptance of family history of previous erythroblastotic infants as indication for induction of labor or radical therapy, it is of importance to examine the records of multiple pregnancies of Rh negative, sensitized mothers. In two families in this series erythroblastosis appeared in the first pregnancy; there was a history of transfusion in one. In 19 families, erythroblastosis occurred first as the second pregnancy, in nine as the third, two as the fourth, seven as the fifth, one as the eighth, and one as the ninth.

Among the families studied, there were 19 pregnancies subsequent to the first erythroblastotic

TABLE VII

CLINICAL FEATURES WITH UNFAVORABLE PROGNOSTIC SIGNIFICANCE
(PRESENT IN 1ST 48 HOURS)

			24 Cases
Liver 3 f.b.	−+−++	+−+−−	1
Edema	−+−++	−−−−−	1
Irreg. Resp.	+++++	−−++−	4
Antib.'s By's Sm	+++++	+−−++	7
Hb<11 gms.	+++++	−−+−−	4
>100 Ebs/100 WBC	−+++?	−++?−	2
	Deaths	Kernicterus	"Normal"

TABLE VIII

RELATION OF SURVIVAL TO NUMBER OF UNFAVORABLE SYMPTOMS NOTED

Survived—Normal	5	13	3	1	0	0	0
Survived—Kern.	0	2	2	0	1	0	0
Died	0	0	0	1	1	1	2
	0	1	2	3	4	5	6
	Number of Unfavorable Symptoms						

infant. These resulted in one normal infant, two abortions, one premature stillbirth, 14 infants with erythroblastosis who recovered and one infant who died of erythroblastosis. Four surviving erythroblastotic infants occurred in families following one fatal case of the disease and six children recovered from erythroblastosis in families where there had been two previous fatalities from this cause. There was no consistency demonstrated in progression of severity with repeated pregnancies.

Table IXa shows a family where the generally accepted sequence of events occurred.

Table IXb also shows a familiar sequence. In this instance the mother may not have been immunized until the fourth pregnancy. Since an OA and an Rh incompatibility existed in the first pregnancy, the competition of antigens postulated by Chappell and Wiener may have delayed Rh isoimmunization. Another family has recently been reported by Dr. Thomas Perry because of the unusually late immunization of the mother (Table IXc).

Another unusual sequence of events is portrayed in Table IXd, the last three infants of whom are included in this series.

After one normal pregnancy there were two infants with severe erythroblastosis fetalis, dying in three days. The ensuing five children all suffered from the same malady but with a general tendency to increasing mildness.

One may conclude that the family history is of little assistance in predicting the outcome of a given pregnancy in a sensitized mother. Even the history of fatal erythroblastosis does not preclude the occurrence of subsequent infants with only mild manifestations, who will readily survive.

Chairman Zuelzer: This point is very important for us and even more so for the obstetrician. Dr. Leonard's experience raises grave doubts as to whether the family history can be used as a single prognostic standard. I have already quoted an example of unwarranted obstetrical interference

TABLE IXa

Father: Rh positive
Mother: Rh negative High anti-Rh agglutinins

1. Normal infant
2. Mild jaundice 6 days
3. Moderate jaundice 1 week
4. Severe jaundice; several transfusions
5. Moderate jaundice and anemia; 5 transfusions

TABLE IXb

Father: Rh positive
Mother: Rh negative

1932—Group A Rh positive. Living and well
1935—Abortion at 5 months
1936—Full term, died in 10 minutes
1940—Group O Rh positive. Living and well
1946—Group O Rh positive. Erythroblastosis
Intense jaundice, slight anemia
Blocking antibodies 1:8
Living and well

TABLE IXc

Father: Group O Rh positive
Mother: Group B Rh negative (agglutinins 1:200)

1927—Group O Rh positive	Living and well
1930—Group B Rh positive	
1932—Group B Rh positive	
1934—Group B Rh positive	
1938—Group B Rh positive	
1941—Group B Rh positive	No neonatal jaundice or anemia
1943—Group O Rh positive	
1944—Group B Rh positive	
1947—Group O Rh positive. Erythroblastosis recovered	

based on this assumption. A second case which has a bearing on our ability to anticipate severe disease is that of an infant who was admitted with mild anemia at ten days of age. The patient proved to be Rh positive, the spleen was somewhat enlarged, the mother's serum contained antibodies with a titer of 1:128 in albumin. The mild course of the baby's illness was in contrast to the history of the preceding pregnancies. After delivering one normal child the mother had one stillbirth, one miscarriage, another stillbirth and again a miscarriage. The sixth pregnancy resulted in the birth of normal, though Rh positive twins. The seventh and eighth pregnancies again ended in stillbirths yet our patient, the product of the ninth, survived with very little medical attention.

TABLE IXd

Father: Rh positive
Mother: Rh negative. Increased antibodies

1933—Living and well
1934—Died at 3 days, erythroblastosis fetalis
1936—Died at 3 days, erythroblastosis fetalis
1938—Erythroblastosis fetalis, living and well
1940—Erythroblastosis fetalis, living and well
1941—Erythroblastosis fetalis, living and well
1944—Erythroblastosis fetalis, living and well

Group O Rh positive, slight jaundice, moderate anemia, hospitalized 13 days, received 380 cc. blood. Living and well

1946—Erythroblastosis fetalis, living and well

Group O, Rh positive, slight jaundice, moderate anemia, hospitalized 13 days, received 185 cc. blood. Living and well.

A third case was that of an infant who appeared clinically well. Erythroblastosis was evident only by a mildly accelerated fall in hemoglobin during the first week of life. The mother earlier had lost a child with severe erythroblastosis and her serum at the time as well as during the recent pregnancy contained antibodies. Our tentative prognosis had been so grave that the family had requested an abortion but fortunately was dissuaded by a conservative obstetrician.

Thus the effects of maternal sensitization on the fetus do not necessarily progress in severity with the number of pregnancies and, as Dr. Leonard has stated, the fate of the individual offspring is almost unpredictable except on a general statistical basis. Here again we need some figures. Table X shows the family histories of our surviving patients. In 18 cases a history of erythroblastosis in siblings was obtained. In 13 of these cases the patient lived although at least one sibling had died of the same disease. In nine instances survival of a child followed the most severe manifestation,

TABLE X

FAMILY HISTORY OF 76 SURVIVING RH POSITIVE PATIENTS WITH ERYTHROBLASTOSIS FETALIS

Pregnancy	No. of Cases without Previous History of E.F.	No. of Cases with Previous History of E.F.	Previous History of Surviving E.F.	Previous History of Fatal E.F.	
				Neonatal	Stillbirth
1	4	0	0	0	0
2	30	1	1	0	0
3	13	8	2	3	3
4	5	2	1	0	1
5	3	3	1	1	1
6	3	4	0	0	4
Total	58	18	5	4	9

namely, stillbirth from erythroblastosis in a previous offspring. This is not to say that the family history is without influence on the outlook. The mortality is certainly higher where evidence of previous sensitization is present than in the group as a whole. Table XI shows data on the outcome of all subsequent pregnancies in 30 women who had previously given birth to an infant with erythroblastosis. In passing we can explain the incidence of normal children on the assumption that they were Rh negative, offsprings of heterozygous or Rh negative fathers. Of the children with erythroblastosis approximately 50% survived. In Table XII even more unfavorable conditions are assumed. Only those pregnancies are considered which followed the first fatality from erythroblastosis. Surprisingly, the fatality rate is only slightly higher than in the previous group.

TABLE XI

PROGNOSIS IN RELATION TO FAMILY HISTORY. OUTCOME OF BIRTHS FOLLOWING E.F. IN PREVIOUS OFFSPRING IN 30 WOMEN

	No. of Cases	Living	Dead
E.F.	51 (88%)	25 (43.2%)	26 (44.8%)
No. E.F.	7 (12%)	6 (10.4%)	1 (1.6%)
Total	58	31 (53.6%)	27 (46.2%)

TABLE XII

FAMILY PROGNOSIS OUTCOME OF 41 BIRTHS FOLLOWING THE FIRST FATALITY FROM RH SENSITIZATION IN 19 WOMEN

	No. of Cases	Living	Dead
E.F.	34 (33%)	15 (36.7%)	19 (46.3%)
No. E.F.	7 (17%)	6 (14.6%)	1 (2.4%)
Total	41	21 (51.3%)	20 (48.7%)

A more complete picture is presented in Figure 6 which illustrates the outcome of all conceptions in women who had had at least one child with erythroblastosis. Surprisingly the graph shows only a slight increase in the incidence of stillbirths in the later pregnancies. If there were an appreciable progression in the severity of erythroblastosis we should find an increasing proportion of stillbirtths in the later pregnancies. The incidence of erythroblastosis of all types does, of course, increase to a peak in the second pregnancy and drops thereafter as does the total number of pregnancies. Yet the proportion of fatalities does not increase materially with the increasing number of pregnancies. We can use figures of this sort to tell the parents of our patients what they can expect on a statistical basis but we cannot predict the severity of the disease in a given infant on the basis of family precedents. Before taking credit for prophylactic or therapeutic measures we must remember that even in groups of patients with such antecedents the chances of survival are in the neighborhood of 50%, and results must be interpreted accordingly.

Next on our agenda are the complications of erythroblastosis. This subject has been neglected in the recent literature and perhaps in practice because of the emphasis on Rh. We are apt to forget that we are dealing with new born babies subject to all the complications of the neonatal period and, moreover with a group which appears particularly susceptible to such complications. Depending on the nature of the complications these patients may require certain measures entirely apart from the specific procedures advocated by various authors. Our data show that complications are a major factor in producing death in erythroblastosis and must be anticipated whenever possible.

Dr. Leonard: The most frequent and serious complication encountered by us was hemorrhage. In an earlier series of 55 patients reported from the New York Hospital 29% showed some hemorrhagic manifestations. In our present series of 47 cases there were 12 who had hemorrhages of some degree, usually not at birth but during the first few days of life. Hemorrhages occurred in the skin, respiratory and gastrointestinal tract, brain, kidneys, peritoneal cavity and heart. Eight of these 12 patients died. The cause of hemorrhages in these patients has not been definitely established. We have felt for some time that they were associated with hypoprothrombinemia but we have insufficient data to prove the relationship. In the only three patients with hemorrhages in whom prothrombin studies were done, the concentration was 48%, 100% and 100%. These patients

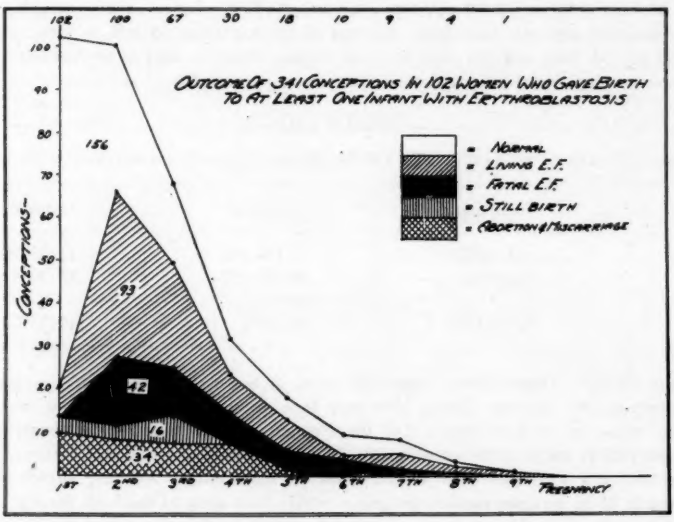
102 100 67 30 18 10 9 4 1
OUTCOME OF 341 CONCEPTIONS IN 102 WOMEN WHO GAVE BIRTH TO AT LEAST ONE INFANT WITH ERYTHROBLASTOSIS
= NORMAL
= LIVING E.F.
= FATAL E.F.
= STILL BIRTH
= ABORTION & MISCARRIAGE
156
93
42
16
34
- CONCEPTIONS -
1ST 2ND 3RD 4TH 5TH 6TH 7TH 8TH 9TH PREGNANCY

FIG. 6

survived. Administration of vitamin K was followed by improvement in some instances but not in others. However, for sometime it has been our practice to give infants with erythroblastosis vitamin K as well as transfusions of whole blood.

Thrombopenia has been suggested as another posible mechanism for hemorrhage in these patients. Our data on this point are not conclusive. Two of our patients with platelet counts as low as 120,000 and 140,000 did not show any hemorrhage.

Chairman Zuelzer: Two patients included in my survey had almost no platelets in their blood. Both had hemorrhagic manifestations and died, whether because of thrombopenia I am unable to say.

Dr. Leonard: Another possible cause for hemorrhage is increased capillary fragility. We have the impression, based on a few observations with the tourniquet test that increased capillary fragility might explain not only hemorrhage but also edema in infants with normal serum protein levels. In any event hemorrhage is important and should be studied and guarded against with every means at our disposal.

Another prominent complication was diarrhea which occurred in 10 of the 47 infants and, though never severe, was often troublesome. It responded to the usual measures.

The next most common complication was infection which occurred in six patients. Two had omphalitis, which led to abscesses, septicemia and death in one case. Pneumonia occurred three times. One infant had bacteremia and abscesses without known portal of entry. Infections not only are

common in these infants but are apt to be severe in character and for this reason our staff has recently adopted routine prophylactic penicillin therapy.

Obstructive jaundice with acholic stools developed in the course of their illness in two or our patients. One of these was subjected to a laparotomy in the hope of finding a biliary atresia but only inspissation of bile in the intrahepatic bile capillaries was found. This patient subsequently died. The other infant showed signs of obstructive jaundice during the second week after having received numerous transfusions in spite of normal hemoglobin levels. He recovered ultimately without evidence of impaired liver function.

Under complications we also included prematurity. Our series includes three infants with birth weights below 2500 grams. Two of these patients died. Of an additional group of six infants weighing between 2500 and 3000 gm. three succumbed. Thus of nine infants weighing less than 3000 gm. five died and only four lived; whereas of the remaining 38 infants with birth weights above 3000 gm. 33 lived and five died. It is our feeling, therefore, that in erythroblastosis the full term infant has a much better outlook than one that is born prematurely.

TABLE XIII

PROGNOSIS IN RELATION TO MATURITY OF 140 ERYTHROBLASTOSIS FETALIS BIRTHS IN 81 MOTHERS

	No. of Cases	Living	Dead
Premature	14 (10%)	2 (14.3%)	12 (85.7%)
Full term	126 (90%)	89 (70.6%)	37 (29.4%)
Total	140 (100%)	91 (65%)	49 (35%)

Chairman Zuelzer: This is a most important point. It has been stated or rather suggested—for to my knowledge no adequate figures have ever been published—that premature delivery is of prophylactic value in erythroblastosis. On the strength of such hints some obstetricians have become quite radical and perform cesarean sections if sensitization in a pregnant Rh negative woman is demonstrated and sometimes even without proof of sensitization. We have already commented on the hazards of an accurate prenatal prognosis which must serve as the basis for the decision to deliver babies with erythroblastosis prematurely. Let us now see how premature babies actually fare in this disease. Dr. Leonard's figures are suggestive but too small. Our own figures on this point are based on 140 patients in whom we were able to get adequate data. Table XIII shows a high incidence of prematurity in infants with erythroblastosis as compared to a random population. Ten per cent prematurely born infants in a group of white patients is in fact so high that one wonders about a possible connection. The 14 premature infants were born spontaneously, without obstetric induction. Certainly this is a more favorable set of conditions than that connected with the hazards, however, slight, of induced labor or cesarean sections. Yet of the 14 premature infants in this series 12 died and 2 lived. This is out of all proportion to our overall mortality and is the reason why we, too, consider prematurity as a complication of erythroblastosis. We consider our figures, small as they are, as a strong deterrent from premature induction of labor regardless of the method used. Perhaps the experience in other clinics has been different but it would take a very large series to convince us that premature delivery is actually advantageous for infants with erythroblastosis.

Two other situations which might be called complications of erythroblastosis to my knowledge have not received any study or attention thus far. Two of our patients had sugar levels of 0 and 7 mgs./100 cc. blood respectively and it was our feeling that the hypoglycemia was a major factor in the death of these (2) infants. I am not prepared to say what the underlying mechanism may be. It is conceivable that either derangement of hepatic function or overproduction of insulin by hypertrophied islets of Langerhans may be responsible. In one case such hypertrophy was actually demonstrated postmortem. We have not yet enough data on hypoglycemia in erythroblastosis but the determination of the blood sugar in our hospital has become a standard procedure in the management of these patients and if hypoglycemia of such degree is encountered it should be corrected. The second condition, often more important than realized in our enthusiasm for transfusion

therapy, is hypothermia. Some of our patients have shown a very marked inability to maintain their body temperature which in several instances fell as low as 33.90-34.4°C. while the patient was exposed for considerable time during a transfusion, I am personally convinced that several of our patients died of what might be called exposure. We are now paying a great deal of attention to this feature and prefer to place infants with erythroblastosis in an incubator.

Let us now consider sequelae. The pediatrician is anxious to know whether the patient who has survived erythroblastosis will be normal as regards mental development and neurologic findings.

We were impressed by the difficulty in predicting during the period of hospitalization the ultimate result as regards neurologic sequelae. Figure 7 is an attempt to show graphically what had happened to a group of 25 patients from 9-77 months after the initial episode. These children had been in our hospital during their initial illness which had met the strict diagnostic criteria given earlier. The re-evaluation study consisted of a complete pediatric history and physical examination. Atten-

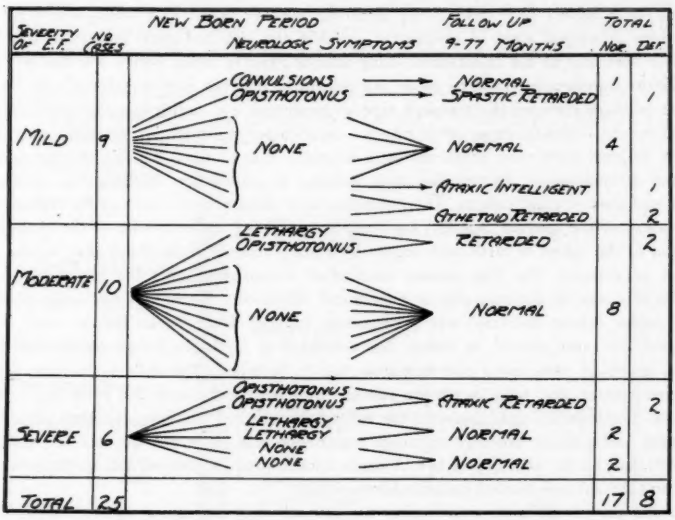

FIG. 7

tion was paid to the usual developmental landmarks such as smiling, sitting, standing, walking and talking. In addition the parents were asked to give us their evaluation. Fifteen of these patients were examined psychometrically by psychologists of the Merrill-Palmer School. Their results checked closely with the impressions gained by the pediatric examination.

The figures are weighted unfavorably because some of these children were brought back to us because of mental retardation whereas many of the presumably normal children did not return. Also the two patients in this group who were below one year were included because they had already shown definite impairment whereas other patients under one year were not included because it was felt that a final evaluation was not yet feasible. The total incidence of sequelae was therefore higher than expected.

The left hand column shows an arbitrary grouping of the cases according to the severity of the initial disease. There seemed to be little correlation between the early picture and the outcome. Four of the patients whose disease had appeared mild later showed signs of mental retardation or neurologic abnormalities or both. There was also little correlation between the early signs and symptoms which might be related to central nervous system involvement and the outcome. Some patients with early neurologic symptoms later appeared normal while others who had given no indication or neurologic disturbances were retarded or had ataxia, spasticity or athetosis. However, all of the four

patients with opisthotonos in the newborn period later developed signs of brain damage. We were impressed by the fact that some of the patients who later were definitely abnormal mentally or neurologically had seemed perfectly normal at three or four months of age or even later. Thus it is difficult to give a final prognosis until the patient is at least one year old and perhaps as we follow the apparently normal children through their further development we may have to revise our figures still further.

Before we hear from Dr. Wheeler regarding therapy there is one more subject which requires discussion and should form the background for our thoughts on treatment, namely a presentation and breakdown of mortality figures.

Dr Leonard: In our group of 47 infants there were 10 deaths, or a mortality of 21%. I should like to break the group down according to the treatment given. In the early part of this study there was still some doubt in our minds concerning the merits of Rh positive versus Rh negative blood for transfusion. Three infants were deliberately given Rh positive blood with satisfactory results in two while the third developed signs of obstructive jaundice and also had gross hematuria which may or may not have been due to the transfusion. Nine infants received blood which was not typed for Rh. One died before transfusions could be given. All remaining patients were transfused with Rh negative blood. Most of these received the standard type of treatment, e.g. multiple small transfusions given as indicated by the blood findings. As a rule we used 20 cc. of blood per kg. body weight. In this group of 38 patients there were seven deaths, a mortality rate of 18%. During the last year a more radical form of transfusion therapy has been gaining in popularity. Exchange or exsanguination transfusion was used in eight infants. These patients were chosen on the basis of the criteria proposed by the advocates of the method; namely, family history, a rising antibody titer in the mother's serum, the condition of the infant at birth with regard to icterus, anemia, erythroblastemia, edema and general clinical appearance. The first patient succumbed immediately after the treatment and it was thought that this was an accident due to mechanical difficulties. There was one other death in this group, an infant whose delivery was prematurely induced four weeks before term. The child weighed 2400 gm. and seemed in rather fair condition at birth. Exchange transfusion was done through the umbilical vein, using approximately 300 cc. of blood. The child's condition grew worse during the next three days with increasing edema, respiratory difficulties and rales in the lungs. On the third day blood studies indicated that the exsanguination had not been complete since sensitized red cells were still present. Another exchange transfusion was given but the child's condition grew worse and he died on the fifth day of life. A major contributing factor to death was hemorrhage from the rectum and the autopsy showed multiple hemorrhages.

Prior to the use of exchange transfusions we had felt that any infant with a nucleated red cell count over 250 per 100 leukocytes had a poor prognosis. No single factor should be considered that important but four of our patients with counts of 260, 410, 800 and 860 nucleated cells per 100 leukocytes survived following exchange transfusion.

The immediate cause of death in eight patients who had received multiple small transfusions was listed as septicemia in two, bronchopneumonia in three and unknown in three instances. The autopsies were performed by various members of the pathology department but the reports and sections were reviewed by Dr. Dooley, the pediatric pathologist. He reported that the finding common to all cases was hemopoiesis, particularly in liver and spleen, also to a lesser degree in lungs, pancreas and other organs. We felt that anemia did not cause death in any case but that infection and hemorrhage were the principal causes of death. However, there remained some patients who showed no pathologic findings other than those of erythroblastosis itself. No agglutinative thrombi were seen on careful search.

Chairman Zuelzer: In comparing mortality figures for a given type of therapy two factors must be considered, one the criteria for selection of cases already discussed here, the other the age and condition of the patients. Almost by definition the patient who receives an exchange transfusion is handed to the pediatrician almost immediately after birth and will have close supervision and the best possible care. Our material differs in that patients were admitted as late as 11 days after birth. The largest number of deaths occurred in the first 48 hours—this is the group presumably dying from erythroblastosis and we might call it legitimate mortality, for which we must accept responsibility. There were other patients, however, who were admitted on the third, fourth or fifth

day or later, often in poor condition. These children should have been hospitalized and treated much earlier. I do not wish to use these figures as an alibi of our mortality rate but to make a point of practical importance. Pediatricians should make every attempt to induce the general practitioners and the obstetricians to refer these patients to them at the earliest possible moment—preferably before they are actually born—so that they can have early supervision and good pediatric care. I am convinced that on the whole this will save more lives than any other single factor in the treatment because it will do away with preventable complications and neglected cases.

Figure 8 is constructed from 81 consecutive, unselected, proven cases of erythroblastosis and indicates our overall mortality and the breakdown according to pathologic findings. Under the particular conditions of the Children's Hospital of Michigan we do not see stillbirths or hydrops but only live-born infants who live at least long enough to reach the hospital. The overall mortality rate, which includes many neglected cases and infants moribund on admission, was 22.2%. Complete autopsies were done in 15 cases by myself or a resident under my supervision. All the sections were reviewed by myself. Our interest was focused particularly on complications and on the anatomic cause of death. Infection, severe enough to be a legitimate cause of death in itself, was present in three

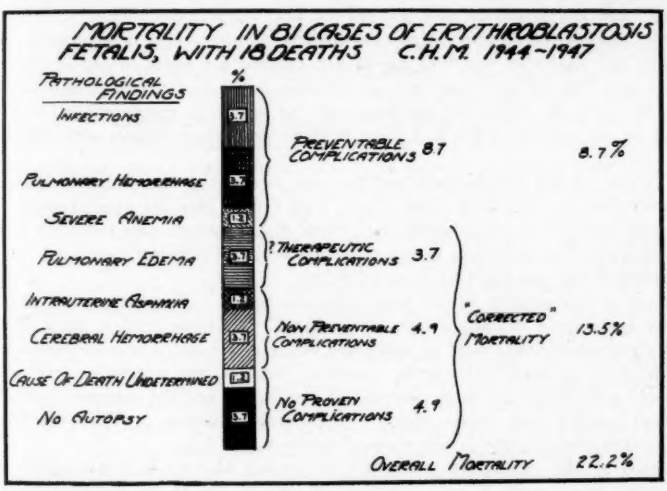

FIG. 8

cases; namely, massive pneumonia, multiple lung abscesses and Str. hemolyticus septicemia. In a sense these are preventable complications. The same might be said about massive pulmonary hemorrhage which occurred in another three patients. I am not sure that I am justified in calling this complication preventable but all three patients died suddenly on the third or fourth day of life when we have reason to believe that the prothrombin level is at its lowest point. Such data on prothrombin as we have show a frequent tendency toward marked hypoprothrombinemia in patients with erythroblastosis. These three patients moreover had not been treated in such a manner as to anticipate hypoprothrombinemia and they died almost immediately after admission.

One patient surely died a preventable death. This infant was born at home, brought to the hospital on the eleventh day of life with a hemoglobin level of 2.4 gm. and died before transfusion could be started.

Three patients had severe pulmonary edema. I am quite uncertain as to whether this finding should be considered part of the disease or as a complication which might be prevented. It was my impression that two of these patients were in good condition until the time when either blood or other fluids were given intravenously and that almost immediately afterwards the signs of pulmonary edema developed and the infants died. For this reason we have become very conservative with respect to the amount of blood or any other fluids given to infants with erythroblastosis. We prefer

to keep these babies slightly dehydrated rather than overhydrated. In any event we can put a question mark after pulmonary edema.

Intrauterine asphyxia (shown by massive aspiration of amniotic fluid at autopsy) and massive cerebral hemorrhage are complications which may be called non-preventable and which we would not expect to be corrected by any form of specific therapy. These are complications of birth rather than of erythroblastosis. In one case we were unable to determine the anatomic cause of death. We must remember that this is not an uncommon situation in the newborn period. In three cases no autopsy was done. Although in one of these there were clinical signs of massive pulmonary hemorrhage and in others evidence of infection I have put this group in the category of "no proven complications" which is part of what I consider the true or "corrected" mortality rate for our series.

It is of interest to correlate these figures with the age on admission and the time of survival of the patients in the hospital. The three patients with infection did not reach the hospital until they were three to five days old and were in fair condition on arrival. The three patients with pulmonary hemorrhage all died on the fourth day. Of the infants with pulmonary edema one died on the first day of life, another on the second, the last on the fourth day, following intravenous therapy. The patients with cerebral hemorrhage died between the first and fifth day.

Kernicterus was present in a very high proportion of the fatal cases. It occurred in all but one of the infants who died after the third day of life, but was not found in any of those dying in the first 48 hours. This strongly suggests a time element in the development of the staining of the cerebral nuclei. It would seem that kernicterus is one of the manifestations of severe erythroblastosis but we did not consider it as a cause of death since many patients with clinical signs of kernicterus survive.

Taking account of the circumstances and the type of material our mortality figures compare favorably with those reported from other clinics. They can be used for orientation by comparing the results with those of exchange transfusions. None of our patients were treated in that manner. It has seemed to us that the benefits of this procedure were still sufficiently uncertain to justify the attempt to establish what you might call a control series.

The analysis of our morality figures then brings out several facts. 1. A substantial part of the mortality rate is the result of complications rather than of the disease itself. 2. Many of these complications are preventable and should be anticipated whenever possible. The most important factor in the management of erythroblastosis under conditions faced by the average general or children's hospital would seem to be the early diagnosis of the disease and the constant close supervision of the patient coupled with certain objective prophylactic measures. 3. The corrected mortality rate for an average group of patients with standard therapy was 13.5%.

In our desire to take nothing for granted we have shown what we hope is a healthy skepticism in regard to the management of erythroblastosis. We would like to end up, however, with some positive recommendations and I have asked Dr. Wheeler to conclude our discussion with an outline of the treatment of erythroblastosis.

Dr. Wheeler: From the slides shown previously it is apparent that babies with erythroblastosis surviving at the end of 48 hours ought by all odds to survive. Table XIV represents a clinician's concept of the pathology and doesn't jibe with Dr. Zuelzer's last slide. It merely represents some

TABLE XIV

LEADING CAUSES OF DEATH IN RELATION TO TREATMENT

Infection	"Premature" type of care
Aspiration	
Anemia	
Hypoprothrombinemia	Anticipate and Modify
Hypoglycemia	
"Toxicity"	?

of the attributable causes of death that we, as clinicians, attempt to prevent. I think we are agreed that two things should not happen: infection and aspiration. In an atempt to eliminate these two preventable causes of death we prefer to admit newly born erythroblastotic babies directly to our premature nursery. Outside of the fact that these babies are not prematures and that the majority of them do not need external heat, the very type of care used for premature babies is the type of care which we ought to have for these babies. In the first place, the nurses in the premature nursery are used to caring for apathetic babies, and in the second place the general arrangement of the premature nursery is designed to keep infection away. Another advantage is that if the baby is cared for by the resident who is caring for the prematures, who is much more apt to go cautiously on the infant's feeding. We would very much rather ease these babies into their initial feeding schedule than to start them out with the amount of formula which the normal newborn is apt to take. I can't stress too much the fact that the general excellence of newborn care is the basic consideration.

What other factors can you anticipate? In the first place, no baby should be allowed to die from lack of hemoglobin. We have been fooled, and perhaps you have too, when confronted with babies that have an adequate hemoglobin level at first but which diminishes almost overnight to an extremely low level. We determine the hemoglobin concentration at least twice a day for the first few days until we think we know what the rate of hemolysis is for that particular baby. When it diminishes to about 12 grams per cent in the first week, we transfuse that baby and bring the level up and maintain it above 12 grams. During the second and subsequent weeks we will allow it to sag to perhaps 10 grams percent. The important thing is that we can be forward looking about this and anticipate anemia and prevent it. What kind of blood should we use? Well, it seems reasonable to use Rh negative blood. We formerly used Rh positive blood on the theory that it would soak up, bind, and eliminate Rh antibody in the baby, but that has been shown not to happen. Our experiments on the release of antibody show that this antibody is released from cells at body temperature, and it is not a firm union. The antibody tends to dissociate from the antigen, and we have data to show that given Rh positive blood, we can abolish the anti-Rh antibody in that baby's serum only temporarily. So we have stopped using Rh positive blood for our major transfusions. However, I wish to make one point here. It is safe to use Rh positive blood, and it will help tide the baby over in an emergency. There is absolutely no excuse for a baby to die of anemia while you are frantically searching for an Rh negative donor. If the baby is anemic enough for you to be worried, transfuse with Rh positive blood. Then you can hunt for an Rh negative donor at your leisure. It seems reasonable to us to use sedimented red cells which will raise the hemoglobin concentration in the baby as much as 4 or 5 gm./100 cc. when 20 cc. of blood are given per kg. of body weight. This practice also avoids the administration of a rather considerable amount of extra sodium which is present in citrated blood and which, at times, has seemed to us to predispose to the development of edema even in the face of a rather normal serum protein concentration. The blood bottle is simply carried to the bedside from the blood bank with care to avoid agitation and is tipped upside down very slowly when the transfusion is to be started. Oxygen is administered continuously in anemic babies until transfusion has been completed.

A low prothrombin is a feature which may be expected in those babies who have severe liver damage. This, of course, can be followed from the laboratory standpoint. We determine prothrombin concentrations at least twice a day for the first three or four days even though we administer Vitamin K on theoretic grounds when the baby is admitted. We know that in severe liver damage Vitamin K often does not prevent the development of hypoprothrombinemia, and we know that once the baby with erythroblastosis develops a low prothrombin concentration, the administration of further Vitamin K will not raise this to normal levels quickly or surely enough to prevent severe hemorrhage. In the face of a low prothrombin concentration we would transfuse whole blood immediately or even use plasma. Dr. Zuelzer transfuses his babies once to begin with in each case hoping that this will prevent the onset of hypoprothrombinemia. Dr. Zuelzer has already mentioned the babies whom he has seen who became cyanotic and apathetic shortly after birth and in whom he has proven a low blood sugar level. Any baby who looks as though he is heading toward shock ought to have a blood sugar level determination. The treatment is obvious.

Toxicity on the other hand is one feature about which we are completely baffled. The term includes manifestations which have been more accurately labeled in those patients who have been autopsied, cerebral edema and hemorrhage, for instance. We had hoped that exsanguination

transfusion might modify the manifestations of toxicity. I am not convinced it has. Dr. Leonard's service and ours have each performed six of these exsanguination transfusions. We attempted to select the cases on the basis of those having the greatest severity. However, only half of these 12, or six, showed three or more of the six unfavorable clinical features which have been mentioned previously. Of these six babies, however, which in restrospect we would consider to have had very little chance of survival with the older methods of treatment, five survived. That is, of course, too small a series to judge by, and I am sure that you will be interested in Dr. Diamond's series when he talks tomorrow. I hope that he will give data of severity comparable to that which we have mentioned here to substantiate his claims. The two deaths that occurred in Dr. Leonard's series both occurred in babies who would not have been expected to die if the above criteria were employed, and I think we have to look on exsanguination as a rather radical procedure and one not without danger. There is no doubt that it is justified in those cases which would not be expected to survive with less radical treatment.

Will exchange transfusion raise the hemoglobin? Yes, it will raise the hemoglobin and satisfactorily so, but simple transfusion will also do this. Will it replace Rh positive blood with Rh negative blood and thus prevent further hemolysis? Yes, it will do this also but in our opinion the jaundice does not have much to do with the causation of illness in the child and in itself is not an extremely undesirable feature. Will it limit the amount of blood that has to be used? In our experience all the patients who have been exsanguinated have had to come back later for refills of blood the same as babies did previously, and the total amount of blood which we have used has been greater than the average amount of blood which we have used in other severely ill patients. Will it raise the prothrombin level? Yes, it will do this, but I am not sure whether or not it will maintain a satisfactory prothrombin level indefinitely. Will it prevent kernicterus? No, it will not. If it would, we would be justified in using it in many cases which we do not now treat by this method. Will it deplete the antibody from the baby and thereby relieve the baby of further tissue damage due to antigen-antibody combination? Yes, it will deplete the antibodies—for about 24 hours. We have several observations, Dr. Leonard has one, and Dr. Diamond has a number that show that the antibody titer of the baby's serum after exchange does go down, but the next day it returns practically to its former level. Where this antibody comes from has not yet been explained, but to really deplete the antibody of the baby would require a number of exsanguination transfusions which we do not advise at this stage. Will it reduce the toxicity? Again we must say that we do not as yet know. We have seen similar good results with rather anemic babies simply by bringing their red cell count up to where it ought to be. It is the opinion of Dr. Zuelzer and Dr. Leonard and myself that we would like to leave with you a critical attitude toward the evalution of not only exsanguination transfusion but of all proposed therapy. Only when such measures are studied in relation to all of the previously discussed phases of the disease can one claim to have demonstrated conclusively that they are superior. In summary, I feel very strongly about the management of these cases: *while erythroblastosis may be a fascinating disease immunologically, don't forget your pediatrics when you go to treat it.*

Chairman Zuelzer: In some institutions such as Dr. Wheeler's own hospital a fairly large number of patients with erythroblastosis are treated. The staff are carefully instructed in team work. Patients are usually admitted early and everything is ready for their care. Under such ideal conditions exchange transfusion may work as well or perhaps better than other procedures. That can only be shown by future studies. In the meantime it is only fair to point out that exchange transfusion calls for experience and facilities which are not available in many places. I wonder if it isn't much safer in such institutions to treat the babies with good standard medical care rather than to refer them as is sometimes done to another institution often miles away where they may arrive in poor condition. This is now sometimes done mainly because of pressure exerted on hospitals and physicians as the result of statements which have been made over the radio or in the press.

Dr. M. V. Adams—Mobile, Ala.: What is your attitude toward breast feeding in infants with erythroblastosis?

Chariman Zuelzer: I see very little theoretic reason to ban breast feedings in these babies. I should

think the amount of antibody excreted with breast milk would be minimal in comparison with that already circulating in the infant's organism. Moreover, it is uncertain how much antibody would be absorbed unaltered by the intestinal tract. There were six breast fed infants in our series who did just about as well as the others. It seems to me that the question hinges on a simple practical point. If the patient is too sick to nurse there is no point in attempting breast feeding. However, if the baby has a mild erythroblastosis I do not believe that there is any real contraindication to breast feeding. There have been cases reported with sudden deterioration and accelerated hemolysis after the start of breast feeding but these can be matched by almost identical case histories of babies who received formulas.

Dr. Wheeler: One must not forget that while the titer of antibody in breast milk may seem insignificant, the baby drinks gallons of it over a period of time. Allowing for only a very small degree of absorption of unchanged protein, there is the distinct possibility that the baby would be exposed to antibody damage at a time when he should be well into convalescence. I would not sanction continued breast feeding.

Question from the floor: Do you have an explanation for the discoloration of the teeth in erythroblastosis?

Chairman Zuelzer: Quite a number of our patients have shown this feature. If severe icterus is present during the period when the enamel for the deciduous teeth is laid down discoloration may be seen when these teeth erupt. The enamel for the permanent teeth is not being laid down during the neonatal period, therefore the permanent teeth do not show discoloration.

We have a series of about 50 cases now and the worst ones in the past have always been those toxic babies who have jaundice but little or no anemia. If we wait to transfuse them, they never have anemia to treat and ultimately expire. Lately we have done exsanguination transfusions on them because in the past the prognosis always seemed so bad. Do you think this procedure is indicated in these cases or would you still wait for the blood picture criteria as given?

Dr. Wheeler: Didn't those of your patients who died have some of the other unfavorable manifestations?

Dr. Erickson: Yes, but they had no anemia. They had the Rh setup, they had antibodies and a positive Coombs' test.

Dr. Wheeler: Even the mildest case will show a positive Coombs' test, but I should think that those of your babies who died even without anemia would probably show marked normoblastemia, hepatomegaly, perhaps edema and some of the other unfavorable signs. Those are the criteria which I think we should use.

Question from the floor: May you not receive a false impression from the hemoglobin determination? As Dr. Erickson pointed out the hemoglobin level and red cell count may be high and yet the baby may die. Could that be the result of lower blood volume resulting in anoxemia?

Chairman Zuelzer: That is a very difficult question to answer because we do not have blood volume studies on these patients. I should think there would be some clinical signs of dehydration before high hemoglobin levels could be interpreted as evidence of hemoconcentration. A low blood volume might be a factor in patients whose hemoglobin level is below 10 gm. and who may have actually a much lower hemoglobin than shown by our usual measurements. When we are dealing with the type to whom you refer, the hemoglobin level is usually 10-12-15 gm. and in such cases I do not believe that enemic anoxia can be a very important factor. I am sorry that I did not show one other slide from our material which shows the hemoglobin level of the fatal cases at the time of death. Except for one patient who died without ever having received medical attention none of our patients died of anemia and in the majority of the cases death occurred when the hemoglobin was at least 10 gm. and sometimes considerably higher.

Dr. C. E. Snelling—Toronto, Ont.: Do you feel that every patient with erythroblastosis should be transfused? For what period of time do you maintain transfusion therapy?

Chairman Zuelzer: We had several patients who never needed a transfusion. As you know in the presence of the serologic findings there may be little clinical evidence of erythroblastosis. In some cases it is only the accelerated drop in the hemoglobin level which indicates that the patient is not entirely normal. We should keep the occurrence of these mild cases very much in mind because of the criticism to which the clinicians have been subjected by some immunologists. One of them has publicly accused certain people of malpractice for not transfusing their patients or for using Rh positive blood. Dr. Wheeler made a very important point when he stated that no patient should be allowed to die for lack of Rh negative blood. Certainly in an emergency Rh positive blood should be given. On the other hand not every baby has to have a transfusion. After all, even this procedure carries a certain risk.

As regards the duration of therapy it is our usual practice to stop transfusing at the end of two to three weeks, to aim for a hemoglobin level of approximately 10 gm. and then to let nature take its course. It has been our experience that after that time the patients do not need further transfusions nor do they need liver or iron. Usually the hemoglobin level becomes stabilized at 7-8 gm. and it is very difficult to prevent the ultimate drop to such a level but by the end of 2-3 months a spontaneous rise takes place. I have yet to see an infant with uncomplicated erythroblastosis whose hemoglobin level did not catch up with that of their contemporaries at the end of six months.

Dr. F. R. Janney—Wauwatosa, Wis.: Would you clarify the point Dr. Zuelzer made about the significance of a rising antibody titer in the mother's blood?

Dr. Wheeler: We have two instances in which the maternal blood showed a definite rise in titer yet the baby turned out to be Rh negative. To my way of thinking the rising titer of antibody does not permit definite conclusions.

Dr. J. R. Hild—Houston, Tex.: In using the hemoglobin level as an indication for transfusion do you depend more on the rate of fall or on the absolute level?

Chairman Zuelzer: It has been our experience that the results are as good or better if we transfuse our patients as the hemoglobin level approaches 10 gm. than if we transfuse indiscriminately while the hemoglobin level is still high. Dr. Leonard reported a case here this morning which I do not which to emphasize too much because of our own warnings against the interpretation of single cases but she had independently arrived at the same impression as I had from two almost identical cases. These patients were transfused every day or every other day without consideration of their hemoglobin level. They probably had increased blood volume and they certainly had very high hemoglobin levels. It so happened that these two patients, like that of Dr. Leonard's, were the ones who developed signs of obstructive jaundice and were shown at autopsy to have severe changes in the liver.

Dr. Leonard: It is our practice also to transfuse on the basis of the hemoglobin level rather than on the rate of fall although we consider a falling hemoglobin as a danger sign. If the rate of fall is rapid we often perform hemoglobin determinations four times a day in order to be sure that the level will not fall to the danger point before we realize it.

Dr. K. J. Ryan—Hollywood, Calif.: If one wants to do an exchange transfusion after 48 hours what is the best method or the best site for administering blood?

Dr. Wheeler: After 48 hours this procedure becomes extremely difficult.

Chairman Zuelzer: My comment would be that if the baby survived for 48 hours he would hardly be a candidate for exchange transfusion. Remember that it is at this period that complications begin to come into play particularly hypoprothrombinemia and hemorrhage.

Dr. Leonard: We have not usually done exchange transfusions in patients who came to us more than 48 hours after birth. In the one instance where a second exchange transfusion was given and even in some of the earlier cases we had some difficulty with the umbilical vein so that our residents now often use the saphenous vein pushing the catheter in far enough so that they get a good pool of blood. Testing the blood before and after the procedure showed that they are getting good exchange.

Dr. C. M. Witzberger—Tucson, Ariz.: What are the minimum diagnostic procedures which you should perform on a baby suspected of erythroblastosis? Do you recommend penicillin prophylactically in the care of patients with erythroblastosis?

Dr. Wheeler: We should determine the Rh "setup" and the presence of antibodies in the mother. In following the baby closely from the laboratory viewpoint the hemoglobin would be the most important measure.

Dr. Witzberger: I am assuming a case where the setup is present, the mother has antibodies but the infant's hemoglobin is satisfactory and there is no clinical evidence of erythroblastosis. How should you follow such a baby before you can feel safe about it?

Dr. Wheeler: If such a patient had erythroblastosis, I would assume it to be mild and would repeat the hemoglobin, blood smear and prothrombin determinations on the second and third day. Another hemoglobin on the fifth and seventh day should tell you in most cases whether the patient has erythroblastosis. I am concerned about those infants whose prothrombin concentration falls on the second and third day and who almost overnight may develop an alarming drop in hemoglobin. Therefore, I would do these two tests at least once a day for the first 3-4 days.

Dr. Leonard: The prophylactic use of penicillin has been a recent routine with us and is based on the frequency of infection which in our experience has been almost always hemolytic Staph. aureus. We felt that penicillin was entirely harmless and we gave 2 daily doses of 2,000 units. In the four or five cases in which this has been done, no infection has developed.

Chairman Zuelzer: I would argue a little with Dr. Leonard about this particular point. I think if penicillin is used as a prophylactic measure it ought to be given in full dosage for a set period of time. I would like to say also that sulfadiazine rather than penicillin would be the drug of my choice because it is apt to affect a wider range of organisms than penicillin.

Dr. Wheeler: If I had only one drug available I would prefer sulfadiazine.
Meeting adjourned.

ERRATA

MARKED HYPOKALEMIA IN PROLONGED DIARRHEA; POSSIBLE EFFECT ON HEART: January, p. 62, paragraph 2 and p. 64, Summary: symbol mM/1. should read mM.

USE OF ALLOXAN IN INFANT CONVULSIONS: March, p. 341: each reference to Figure 2 should read Figure 3; p. 344: reference to Figure 3 should read Figure 2.

PENICILLIN THERAPY OF LATE CONGENITAL SYPHILIS: May, p. 616, Spanish Abstract, paragraph 3, lines 4 and 5 should read: 100 injectadas intramusculares iguales, practicadas cada dos o tres horas de intervalo noche y dia durante ocho o mas dias.

TESTIMONY ON S. 1290 PREPARED FOR THE HEALTH SUBCOMMITTEE OF THE SENATE COMMITTEE ON LABOR AND PUBLIC WELFARE, March 9, 1948: May, p. 667, signature omitted: Jonn P. Hubbard, M.D.

Pediatrics

VOLUME 1 JUNE 1948 NUMBER 6

SPECIAL FEATURE SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

EDWARDS A. PARK, M.D., *Editor*

ONE of the outstanding defects in our medical care system at the present time lies in the isolation of the medical schools which regard their educational obligations as confined to their medical students, to themselves, and to the abstract world. The result is that as soon as medical students become practicing physicians, they are cast adrift and obliged to rely on medical literature, occasional medical meetings and, it should be included, their contacts with the detail men from the drug houses, in order to keep abreast of medical progress. But medical practice is so time-consuming and exhausting that, when the day is done, there is left little leisure or spirit to study and there is no means at all, or very inadequate means, to come into personal contact with the special students of disease, the men who have had the opportunities to work on special problems until they have become authorities. It is because of the aloofness of the medical schools that the practitioners of the country become so dependent on representatives of the drug houses. But the physicians of the country are extraordinarily eager for new knowledge—the difficulty does not lie in any lack of desire—and this is illustrated so splendidly each year at the Academy of Pediatrics' meetings by the avidity with which our own members seek out the panel discussions at which eminent scholars, the country over, present their information and experience. Panel discussions, such as the Academy specializes in, afford opportunities to meet the authorities face to face. But panel discussions are only occasional and they are only substitute mediums for the transfer of facts and ideas. The most satisfactory medium is personal contact and discussion between the specialists on the one side, and the practicing physician, on the other, over a case. Perhaps the greatest benefit which could be brought to pass in medical care in this country would result if the medical schools could be made to descend from their ivory towers—to use Dr. James Wilson's methaphor—and extend their educational facilities to the practicing physicians of the country and to assume the task of keeping them informed as a full part of their responsibilities.

Dr. Kaiser's account of what has been done by the University of Rochester and its

allied hospitals for the rural hospitals and for the physicians of the rural communities is not just interesting, it is thrilling; it is not just an ordinary experiment in medical care, it is a magnificent experiment which is bound to have great consequences, for it is so right and has been so successful that it is bound to have important consequences. In an address before the New York Academy of Medicine which was reprinted by the *Journal of Pediatrics* (31:3, 1947), I express the hope that the new system of medical care which we now see developing sporadically on all sides in this country could be formed around the medical schools as the educational and inspirational centers and I also expressed the view that the medical schools could be the most powerful factor of all in lifting up the general level of medical care the country over. In Rochester, N.Y., the entering wedge has been driven.

Dr. Kaiser's communication is followed by a letter from Dr. George Whipple, the Dean of the University of Rochester and one of the most remarkable personalities in medical education and science of today. It is interesting that Dr. Whipple's letter points out the benefits which have come to the University of Rochester Medical School from the Rochester program as well as the advantages accruing to the outlying hospitals and physicians. It is obvious that entrance of the medical schools into the medical care system of the country will be an example of casting bread upon the waters.

E. A. P.

AN EXPERIMENT IN IMPROVING MEDICAL CARE IN RURAL AREAS ON A REGIONAL BASIS

By ALBERT D. KAISER, M.D.
Rochester, N.Y.

FOR nearly 20 years, the Division of Rural Hospitals of the Commonwealth Fund, an endowed organization devoted "to the welfare of mankind," had concerned itself with the building and developing of general hospitals in small communities. Experience had shown that small communities do not ordinarily have in their midst the trained persons and educational resources to enable hospital and medical practice to attain the development reached in large medical centers. Therefore, an experiment was set up to work out a method whereby the existing resources of small communities can be supplemented and integrated into a close working relationship among themselves and with a large community functioning as a regional medical center.

To implement this experiment the Council of Rochester Regional Hospitals "a voluntary association of hospitals and their medical staffs in the interest of good hospital and medical care" was set up. The problems of medical care which exist outside of hospitals are of great interest to the Council. However, at the beginning, the Council's program centers around the hospital as the nucleus of medical service. It is anticipated that the principles of regional administration developed in connection with hospitals will apply to public health and the broader aspects of medical care. The economic aspect of medical care as related to payment for service is entirely outside of the scope of the Council program.

A sum of $275,000 per year for five years is made available for the experiment. The annual contribution from Rochester funds is $10,000. Of this total of $385,000

an annual sum of $200,000 is allocated to capital improvement of small community hospitals, and $85,000 to education, advisory services and administration.

The region includes 11 counties in the trading area of Rochester. It contais a medical school, six urban voluntary hospitals, and 26 general hospitals outside of Rochester. Full membership is limited to community hospitals owned and operated by unofficial, non-profit associations and providing general care for acute illness. Associate membership with non-voting representation on the governing and advisory bodies and with all benefits except grants for capital improvement is offered to governmental hospitals and to hospitals operated for profit.

FIG. 1

A Board of Directors, mostly laymen, guides the affairs and makes the policies for the Council. It is composed of two delegates from the governing board of each member hospital, and one lay public representative from each county who has no direct connection with any hospital.

Two delegate bodies advise the Board of Directors, namely the Administrator's Conference and the Medical Conference. The Administrator's Conference, composed of the hospital administrators and their alternates, serves as a forum for the exchange of information on hospital administration. It also studies methods to solve common problems, and recommends policies and projects for the consideration of the board. The Medical Conference has a similar purpose as related to medical practice and problems centering around hospitals. It is composed of one physician and one alternate physician elected by the medical staff of each member hospital.

The executive staff is made up of the executive director, a physician who serves

on a part-time basis, a full-time associate director, who is also a physician, a business manager, a director of nurses (part-time), a public relations assistant and secretarial assistants. The executive staff is assisted by consultants in hospital administration, medical education, public health, nursing services, accounting and purchasing services.

In order to obtain broad interest in the regional medical experiment, several committees emanating from the Board of Directors, Administrator's Conference and Medical Conference are actively engaged in promoting studies and improvements in their respective fields. These committees initiate their own activities and are assisted in their work by members of the executive staff. The numerous meetings conducted by the committees and the larger conferences have brought the men and women of the rural hospitals into friendly and helpful relationships with medical and lay members of the

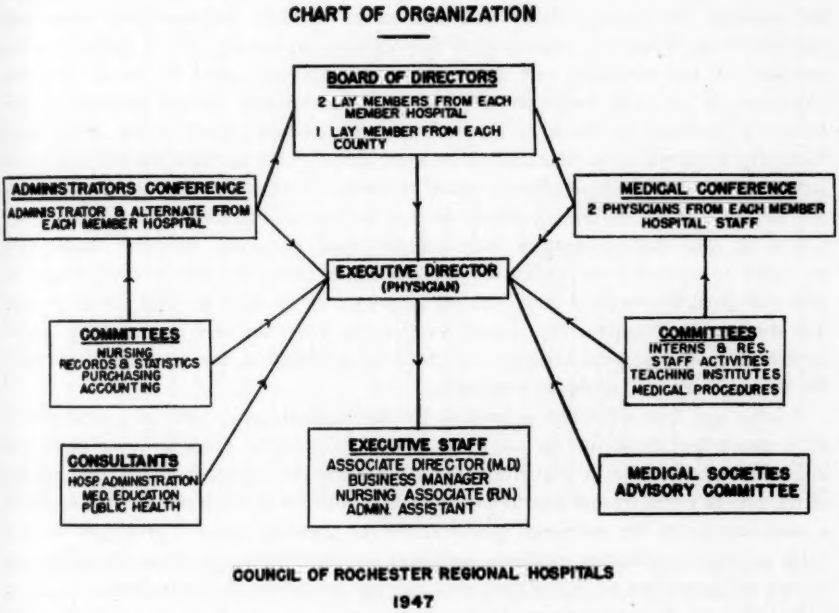

CHART 1

urban hospitals. This accomplishment has contributed immeasurably to the success of the regional experiment.

Before offering the member hospitals services concerned with the administration and with professional activities, hospital surveys were conducted by the executive staff. These were primarily concerned with the operation of the hospital, organization and activities of the governing board and medical staff, and thorough investigation of the functioning of the hospital, department by department. Such surveys were made at the request of the governing board and findings and recommendations were reported only to the board of the hospital concerned. The completed surveys revealed the deficiencies that existed in each member hospital and directed the program that was outlined to improve the services that might assure better medical care.

Hospital administration in the small hospital varies greatly depending upon the competency of the administrator. Early in the regional experiment a college credit course in hospital administration was given at the University of Rochester in which prominent hospital administrators participated. Assistance was given to area hospitals in various administrative departments such as accounting, hospital records, reports, statistics, purchasing, personnel service, nursing and other related services. Employees of the small hospitals were given fellowships for specialized training or consultants were sent to the small hospitals from the large urban hospitals. Significant changes and improvements were brought about in the important field of hospital administration. Space will not permit a detailed account of the progress that has been made in the administration activities of the rural hospital during the last year and a half.

Of paramount importance to the physician is the program that has been developed for assisting the medical group and the nurses in their hospital and community responsibilities. From the beginning of the regional experiment it was evident to the members of the executive staff that little or no progress could be made with the physicians in the rural hospitals unless they were convinced of the sincerity of the assistance proffered by the large hospitals and the medical school in the urban area. Naturally, there was some hesitation to associate themselves with their medical colleagues from the big city if such an alliance would result in dictation and ultimate control from the medical center. Refraining from coercion or pressure methods, opportunities for individual and staff advantages were offered rural hospitals. Hospital staffs were requested to present their needs and assurance was given that no services would be provided from the medical cented unless requested by th rural hospital. Once assured that this regional hospital experiment was entirely voluntary and that nothing would be forced upon a hospital or upon any group in the hospital, the educational program for the medical staff could be undertaken.

Among the first activities undertaken by the medical group was the appointment of a committee of doctors to set up a manual of medical procedures to guide the individual physician in the performance of his routine duties, both in the interest of the patient's welfare and for the professional reputation of the hospital. This involved a consideration of the minimum qualifications for granting hospital privileges in such fields as surgery, obstetrics, medicine, radiology and anesthesiology. These model policies are not obligatory but are stimulating staff members to elevate their standards.

To offer the doctor practising in the rural areas assistance from the medical center presents some difficulties. In some instances physicians resent the inference that they need instruction or guidance in their daily problems, while in other situations the fear exists that physicians associated with urban hospitals coming to the small hospital will threaten the relationship that exists between physician and patient. Nevertheless, it is gratifying that the medical staffs of all of the member hospitals invited professional educational assistance from the hospitals in the medical center.

In any experiment conducted to improve the character of medical care in an area it is essential to have reasonably accurate information on the death rates where the kind of care rendered may have played a part. Such a study was prepared by tabulating the deaths in the various hospital areas in the three years prior to the regional experiment. Ultimately, similiar studies will be made on the death rates in the same areas to determine what, if any, effect the new educational facilities may have exerted on

the medical practice of each community. Information made available to each hospital staff on such diseases as appendicitis, herniotomy, diabetes, prematurity, accidents, etc., brought directly to the attention of each physician how his hospital area compares with comparable institutions in the management of the common medical and surgical procedures.

Obviously the hospital area with a death rate charged to appendicitis that is twice as high as that of a neighboring hospital area should be stimulated to have its staff

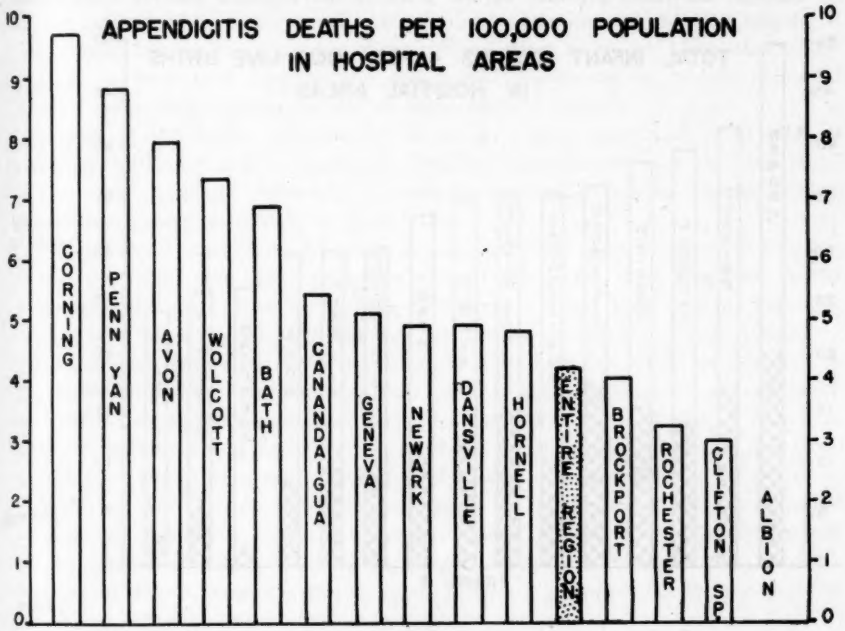

FIGURE 2.

investigate the diagnostic and surgical procedures practiced in that hospital area. Similarly the hospital area in which the death rate of infants under one year of age is twice as high as in a neighboring area invites a thorough analysis of hospital facilities for the care of the newborn and especially the organization for the care and follow up of the premature baby. Making these indisputable data available to each hospital staff points out the desirability of improving certain professional services in the hospital and in the community.

The establishment of clinical conferences in the small hospitals was gratefully accepted. Through a medical committee of the Regional Council, monthly staff conferences were arranged in each of the rural hospitals. Eminent physicians in all fields of practice were sent from the medical center to the small hospitals. The visiting clinician spends half a day with the small hospital staff to discuss a number of problem cases and then makes ward rounds with some or all of the staff members. The success of these clinical conferences and the good will established between the small and large hospitals has more than justified this procedure.

A more formal medical service known as a teaching institute has been offered to a small hospital where requested. These institutes limited to one broad subject covered from several viewpoints, e.g., liver disease discussed by a surgeon, a medical man, a physiologist and a pathologist are made available to the small hospital staff by sending a team of medical teachers to the hospital. The choice of subjects is in the hands of the local physicians. Nursing institutes conducted along the same lines with appropriate subjects are offered the nursing staff of the small hospital.

Through the funds provided by the grant to the Regional Council medical and

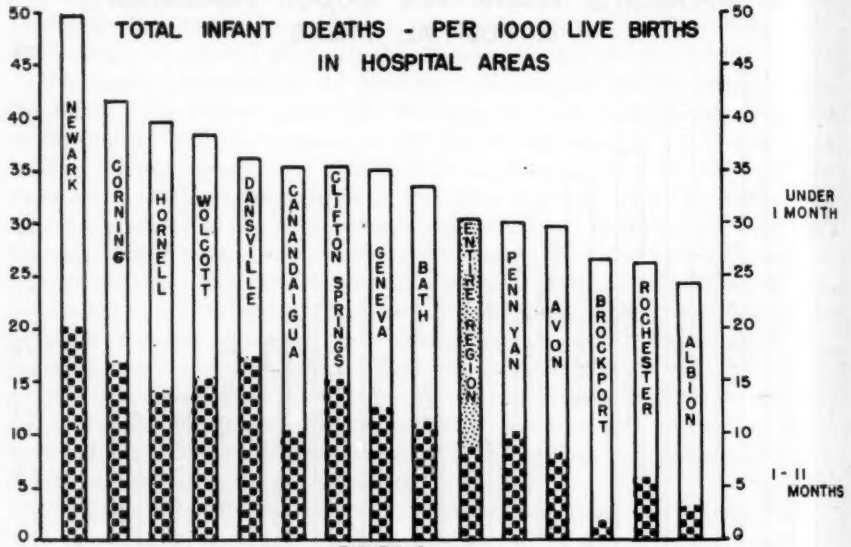

FIGURE 3.

C.R.R.H.

nursing fellowships are offered to appropriate people in the small hospitals. They provide a monthly stipend for training in the large hospitals of the region.

Experience has shown that the busy doctor in the small town or in the country finds it difficult to leave his practice for long periods. The doctors, however, request short courses lasting a week on particular subjects such as newer diagnostic procedures and approved methods of therapy. To meet this request the staffs of the larger urban hospitals have prepared a number of these short courses which have been enthusiastically received.

None of the area hospitals except the large institutions had a resident staff. Because a resident staff is of great and obvious value to the hospital, the Regional Council undertook a program of rotation of a series of interns and residents from the large city hospitals to the smaller hospitals for periods of from two to three months. This program was approved by the Council on Medical Education and Hospitals of the American Medical Association. The rotation of interns or residents has been in progress for over a year in one hospital and for a shorter period in three other hospitals. This rotation of house staff from the parent hospital in the medical center

to the small hospitals of about 100 beds has proved beneficial to the area hospital. Difficulties naturally arise on the part of both parent and recipient institution but these obstacles are gradually being overcome. The experience gained by the intern or resident in the small hospital has proved valuable. A better understanding of the problems of the rural area is obtained by the young doctor, and the presence of a resident physician in a small hospital stimulates the visiting staff to a keener interest in the patient care. Improvement in hospital records is apparent, autopsies have increased and routine staff rounds have been instituted. The parent hospital supervises the training of the resident while in the small hospital, and a committee of the rural hospital is held responsible for the proper use of the rotating intern or resident. Extension of this program to more rural hospitals and greater participation on the part of the small hospital staffs should ultimately lead to better hospital practices.

Surveys in the region revealed deficiencies in certain specialized fields such as radiology, pathology and in anesthesia. Qualified physicians are not available in all of the small hospitals. Where it was possible consulting services emanating from the medical center are offered in these fields.

Though blood transfusions are given in many indicated cases in the small hospitals it was discovered that blood therapy was used many times more frequently in the large urban hospitals. Lack of facilities to conduct a blood bank and to obtain the right type of blood for all needs has restricted the use of blood in the small hospitals. Plans are now complete to conduct a regional blood bank for all of the hospitals in the Rochester Region. The American Red Cross is financing this central bank which will make available to all the hospitals the type of blood that is needed. A competent technical staff located in Rochester will assist the area hospitals in utilizing this blood on the same basis that is now practiced in the large urban hospitals.

With full knowledge of the personnel needs in the region, it has been possible to place young physicians in areas where well trained physicians are urgently required. As the experiment develops and the advantages of rural practice under more favorable hospital conditions become known to young doctors it is hoped that the placement of physicians will aid some of the needy areas.

Insufficient time has elapsed to evaluate the efforts to assist the rural physicians in their home and hospital practice. It is quite clear to the executive staff of the Council that the practicing physician in many small communities has rendered excellent medical care in and out of the hospital. The advantages and facilities are generally inferior to those of the urban area and difficulties arise which cannot be easily overcome. Some of these deficiencies can be corrected by the small hospitals themselves, others can be solved by closer association with the medical center.

The urban hospitals and the medical school have the facilities and the personnel to assist the small institutions within a certain area if they are willing to make them available. It is equally important for the small hospitals to seek these services. If this voluntary relationship can be established it will not only assure better small hospital functioning but also will improve medical care in the local community.

29 Buckingham Street

COMMENT ON VALUE OF MEDICAL SCHOOL PARTICIPATION IN A REGIONAL HOSPITAL AND HEALTH PROGRAM

By GEORGE H. WHIPPLE, M.D.

1. Value to Regional Area, especially rural.
   (a) Clinical conferences conducted in the small hospitals by medical teachers benefit the physicians in these hospitals and keep them informed on newer developments in clinical medicine.
   (b) Short courses given in the medical school and in larger hospitals permit a limited number of physicians to renew their affiliations with a teaching hospital for a short time and to inform themselves in the newer techniques applicable to their daily work.
   (c) Administrative officers, laboratory directors, record librarians, dietitians and other trained workers in the medical center can be of great assistance to individuals responsible for similar tasks in small hospitals.
   (d) Rotation of residents or assistant residents for two or three months to hospitals without any resident staff, brings valuable assistance to the staff of a small hospital. Residents under the supervision of a parent hospital stimulate more careful hospital services such as physical examinations, laboratory procedures, medical records, autopsy permissions, regular ward rounds, etc.
2. Value to the medical school or large urban hospital.
   (a) Establishes better relationship with area hospitals.
   (b) Encourages the small hospitals with limited personnel and facilities to send problem cases to the medical center.
   (c) Familiarizes the staff, visiting and resident, with the medical problems of the rural areas. It promises to solve at least in part the complaint that large areas in the country have inadequate medical care.
   (d) Benefits the residents who spend a few months in a rural hospital by their contact with general practitioners. Will encourage well trained young physicians to investigate the advantages of practice in smaller communities instead of locating in over-supplied areas in big cities.

Already four able young physicians from the Medical School have settled in small towns where they will help to improve the type of practice in their new communities.

TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

By JOHN P. HUBBARD, M.D., *Contributing Editor*
Washington, D.C.

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

BUDGET OF THE U. S. PUBLIC HEALTH SERVICE

(Fiscal year July 1, 1948, to June 30, 1949)

WE HAVE previously reviewed the Federal funds now available specifically to support various aspects of medical education.* To a large extent, financial support for teaching is inseparable from grants awarded for fellowships and research projects. Since the Public Health Service has large sums of money available for fellowships and research, the total budget of this Federal agency should be reviewed in order to appreciate the full extent of its various activities.

The appropriations mentioned below were approved by the House in House Bill 5728. This bill is now before the Senate Appropriations Committee which will make its recommendations to the Senate. If the Senate should adopt any amendments (which is not unusual for appropriation measures), the bill will then be referred to a joint conference committee to work out agreements acceptable to both branches of Congress.

NATIONAL INSTITUTE OF HEALTH

The National Institute of Health not only conducts intramural research in a wide variety of fields but also conducts programs of fellowships and grants-in-aid for general medical research in universities, hospitals and other public and private institutions. It is from this source that the Academy of Pediatrics received a grant of $231,400 for research in "child care health service."

For the next fiscal year the House approved $13,670,000 which includes an increase over last year of $2,667,125. Included within this appropriation is a total of $400,000, increasing by $250,000 the funds earmarked for research fellowship grants in order to enlarge the supply of trained research personnel. Also, included within the total budget increase is $1,382,500 for additional research in diseases of the heart and circulatory system, with provision for research grants-in-aid, direct research by the Institute, and research fellowship grants.

NATIONAL CANCER INSTITUTE

The program of the Public Health Service in the field of cancer includes cancer research in the National Cancer Institute, grants-in-aid to other institutions and to individuals for cancer research, the training of research workers, the training of physicians in the

* PEDIATRICS, 1:426, 1948.

diagnosis and treatment of cancer, loans of radium to hospitals, cancer education, and finally, assistance to state agencies in the prevention, control and eradication of cancer.

The appropriation recommended by the House is for $14,000,000, the same amount approved for cancer work last year. During the fiscal year ending June 30, 1948, the Cancer Institute has been able to grant approximately 100 research fellowships with allocations of approximately $300,000. The House has increased this item by $100,000 for the next fiscal year.

The House Appropriations Committee has also approved an additional $8,000,000 over and above the $14,000,000 appropriation "for drawing plans, erection of buildings, and acquisition of land therefor for research and training projects related to cancer."

Mental Health Program

The House Appropriations Committee deferred action on all fund requests for mental health activities under the Public Health Service pending further study of requirements in this field. Particular scrutiny is now being given by the House Appropriations Committee to that part of the program which calls for state mental health programs.

Control of Tuberculosis

A Federal aid program in the field of tuberculosis is being conducted by the Public Health Service in cooperation with state and local health departments, voluntary associations and agencies, private laboratories and corporations. The program anticipates examination of the entire population of the United States within five years and a complete preventive and public health control program against tuberculosis. Particular emphasis is given to the application of BCG vaccination for the prevention of tuberculosis

The House approved an appropriation of $9,291,000, which includes an increase of approximately $1,000,000, part of which is to provide for training of qualified personnel from state and local health departments in advanced treatment methods and technics.

Control of Venereal Diseases

The venereal disease program is one of the activities which the Public Health Service has been conducting most vigorously during the past ten years. During this period syphilitic mortality per 100,000 population decreased from 16.2 in 1936 to 9.3 in 1946; infant mortality from syphilis per 1,000 live births decreased from 0.73 in 1936 to 0.25 in 1945; the number of babies reported born with congenital syphilis decreased from 18,000 cases in 1941 to 12,000 cases in 1947. Notable decreases occurred also in the admissions to mental hospitals due to syphilis.

The House approved $17,230,000 for the next fiscal year for continuation of the venereal disease program.

Control of Communicable Diseases

The Public Health Service, in cooperation with the states, conducts a program for the control of communicable diseases, with emphasis upon diseases of tropical origin including typhus, plague, and malaria.

The 1949 appropriation approved by the House is $7,490,000 for this program.

Hospital Construction Program

The Hospital Survey and Construction Act (Hill-Burton program) has two broad purposes: (1) to assist the states in surveying their hospital and health facilities and in planning to meet the needs revealed by this survey, and (2) to assist the states in the actual construction of hospitals, health centers, and related facilities. Congress authorized grants of $3,000,000 for survey and planning and $75,000,000 a year for a five-year period for construction. Since each Federal dollar must be matched by $2 of funds from state and local sources, the overall five-year program amounts to $1,125,000,000. The Sugeon General has estimated that this will meet only about 13% of the total need. For the fiscal year commencing July 1, 1948, the House allowed new contract authorizations for $75,000,000.

Grants-in-Aid to States

In addition to the appropriation for special categories such as those mentioned above, the Public Health Service has a general appropriation item for assistance to states in establishing and maintaining adequate public health service through grants, consultative services, demonstrations, and industrial hygiene investigation and training. The House approved an appropriation of $13,865,000 for general public health work other than in the field of mental health.

Construction of Research Facilities at Bethesda, Maryland

The House appropriations bill authorizes the construction of a $40,000,000 combined hospital and research building, together with various auxiliary facilities at the National Institute of Health for general medical research, including research on cancer, cardiovascular and mental diseases.

Salaries and Other Expenses of the Public Health Service

The House allowed $4,047,700 for the overall management functions of the Public Health Service, the vital statistics, and other operating divisions which function in specialized public health fields. An additional appropriation of $350,000 was approved for the liquidation of the Bolton Nurses Training Act, a war-time measure, the purpose of which was to increase the number of graduate nurses.

An appropriation of $285,000 was approved for activities in international health relations.

* * *

By way of recapitulation the House Appropriations Committee has approved the following appropriations and authorizations for the Public Health Service for the year July 1, 1948, to June 30, 1949:

National Institute of Health	$ 13,670,000
National Cancer Institute	14,000,000
Building Construction	8,000,000
Control of Tuberculosis	9,291,000
Venereal Disease Program	17,230,000
Control of Communicable Diseases	7,490,000
Hospital Construction Program:	
New contract authorizations	75,000,000
Administrative Expenses	1,300,000

Grants-in-aid to states	13,865,000
Construction of Research Facilities at Bethesda, Md.	40,000,000
Salaries and Other Expenses	4,047,700
Liquidation of the Bolton Nurses Training Act	350,000
Activities in international health relations	285,000
Operation of Hospitals	21,443,000
Foreign Quarantine	3,000,000
Federal Employees Health Services	392,500
Commissioned Officers' Pay (retired, in training, and on special detail)	1,866,300
Total	$231,230,500*

A recent compilation of grants awarded by the Public Health Service for research projects has been reported by Dr. C. J. Van Slyke, Chief Research Division of Grants and Fellowships.† This report lists the Public Health Service awards made between January 1, 1946, and August 31, 1947, which total $10,214,174. Six hundred and twenty-nine scientists in 193 institutions are sharing in these grants which support research projects in 97 universities and colleges and in 34 hospitals and clinics.

In addition to grants for research projects, other grants are awarded by the Public Health Service for research fellowships "to encourage promising students, interested in becoming proficient in research in medical and related sciences."

As of present date, there are 225 fellows on duty at the institutions of their choice and 131 whose term of service has not yet begun, a total of 356 fellowships, active or pending.‡

The stipend for these fellowships is $1,200 to $1,600 a year for qualified applicants with a Bachelor's Degree, $1,600 to $2,000 for those with a Master's Degree and $3,000 to $3,600 for those with a Doctor's Degree; the higher figure in each case applies to those with dependents.

* Subsequent to the compilation of these figures, the House Appropriations Committee reported favorably on a proposed appropriation of $10,278,000 for the National Mental Health Program. This includes $3,250,000 for research and for training of mental health personnel and $3,550,000 for grants-in-aid to states. Also included in the bill is an appropriation of $1,000,000 to enable the Public Health Service to set up facilities to work in cooperation with the States, dental societies, and other organizations to demonstrate the efficacy of topical application of sodium fluoride to the teeth as a preventive against dental decay. In addition a special appropriation of $700,000 has been made to enable the Public Health Service to inaugurate an emergency program involving disease and sanitation investigation and control in Alaska.

† Van Slyke, C. J., Research Grants Awarded by Public Health Service, Supplement No. 205 to the Public Health Reports (Jan.) 1948.

‡ Personal communication to the author from Byron C. Brunstetter, Ph.D., Chief, Office of Research Fellowships, National Institute of Health, U. S. Public Health Service (April 27, 1948).

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

LEONA BAUMGARTNER, M.D., *Contributing Editor*

INCIDENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES

March 28-April 24, 1948

NUMBER OF REPORTED CASES OF 9 COMMUNICABLE DISEASES IN THE UNITED STATES DURING THE 4-WEEK PERIOD MARCH 28–APRIL 24, 1948, THE NUMBER FOR THE CORRESPONDING PERIOD IN 1947, AND THE MEDIAN NUMBER OF CASES REPORTED FOR THE CORRESPONDING PERIOD, 1943–47

Division	Current period	1947	5-year median	Current period	1947	5-year median	Current period	1947	5-year median
	Diphtheria			Influenza[1]			Measles		
United States	610	922	922	10,095	120,721	8,650	102,680	28,280	104,809
New England	21	47	32	7	225	108	5,840	7,076	7,487
Middle Atlantic	63	165	163	72	119	72	20,492	4,328	20,955
East North Central	86	118	166	80	3,868	427	29,616	5,055	26,395
West North Central	39	85	70	114	14,564	108	7,401	1,444	7,441
South Atlantic	124	170	131	2,878	36,811	2,486	5,349	4,369	7,035
East South Central	54	88	85	635	9,740	606	2,161	1,465	3,182
West South Central	90	127	152	5,279	48,582	4,277	11,332	2,070	5,963
Mountain	75	49	50	664	4,946	609	5,269	1,401	4,643
Pacific	58	73	125	366	1,866	344	15,220	1,072	7,945
	Meningococcus meningitis			Poliomyelitis			Scarlet fever		
United States	285	383	794	126	112	111	8,312	9,898	17,096
New England	10	12	39	0	2	2	916	899	2,211
Middle Atlantic	52	57	155	16	20	19	2,374	2,769	5,679
East North Central	61	85	152	19	13	10	2,645	2,971	4,247
West North Central	21	37	72	19	9	5	595	824	1,552
South Atlantic	48	68	122	16	9	9	463	645	1,340
East South Central	37	38	68	6	9	9	187	419	475
West South Central	25	45	73	31	18	20	197	195	492
Mountain	10	6	10	5	1	3	287	395	855
Pacific	21	35	103	14	31	21	648	781	1,067
	Smallpox			Typhoid and paratyphoid fever			Whooping cough		
United States	7	38	54	225	161	241	8,001	10,545	10,035
New England	0	0	0	24	24	9	532	824	932
Middle Atlantic	0	13	0	16	15	37	915	1,738	1,738
East North Central	0	3	7	24	18	27	1,199	2,110	1,476
West North Central	3	2	8	15	13	10	516	318	318
South Atlantic	2	0	2	58	26	52	1,084	1,363	1,533
East South Central	0	5	4	22	16	23	326	588	463
West South Central	0	15	8	48	25	40	2,172	2,313	1,160
Mountain	2	0	2	1	4	15	659	324	474
Pacific	0	0	6	17	20	20	598	967	967

[1] New York, North Carolina, and Pennsylvania excluded; New York City and Philadelphia included.

Data furnished by the Division of Public Health Methods, United States Public Health Service.

Diseases Above Median Incidence

Influenza.—The reported number of cases of influenza dropped from 25,459 during the preceding 4 weeks to 10,095 for the 4 weeks ended April 24. Of the total cases Texas reported 4,393, South Carolina 1,486, and Virginia 1,138—70% of the total cases occurred in those three States. The recent rise of this disease has been confined to States in the Southern and Western sections of the country. In the East South Central, Mountain and Pacific sections the incidence has dropped nearly to the level of the preceding 5-year median, but in the South Atlantic and West South Central sections the numbers of cases are still relatively high. The incidence for the country as a whole was less than 10% of the 1947 figure for the same weeks, but it was about 17% above the 1943-1947 median incidence. The peak of the recent outbreak was reached during the month of January while the peak of the 1947 epidemic was not reached until March, with very little drop in the number of cases during the month of April.

Poliomyelitis.—While the number of cases of poliomyelitis was not large, it represented an increase of more than 10% over the median for the preceding five years, and with the exception of the year 1945, when 128 cases were reported for these same 4 weeks, the current incidence was the highest for the corresponding weeks in the 20 years for which data are available in this form. Each section of the country except the North Atlantic, East South Central, and Pacific sections reported an excess of cases over the normal seasonal median. While an increase of this disease may be expected at this season of the year, in most preceding years the increase has not occurred until sometime during the month of May; the lowest incidence of the season has normally been reached during the four weeks corresponding to the period under consideration.

Diseases Below Median Incidence

Diphtheria.—For the four weeks ended April 24 there were 610 cases of diphtheria reported. The median number for the preceding five years was 922. For the country as a whole the current incidence was the lowest on record for this period. In the Mountain section the number of cases (75) was 50% above the seasonal expectancy, but in all other sections the incidence was relatively low.

Measles.—The number of reported cases of measles rose from 83,160 during the preceding 4 weeks to 102,680 during the current 4-week period. The incidence was 3.6 times that reported for the corresponding period in 1947, but it was slightly below the median for the preceding 5 years (104,809) cases. Significant increases over the normal seasonal incidence were reported from the East North Central, West South Central, Mountain, and Pacific sections. In other sections, the incidence was about the same or below the preceding five-year medians.

Meningococcus meningitis.—The number of cases (285) of meningococcus meningitis was less than 75% of the number reported for the corresponding period in 1947 and about 36% of the median for the preceding five years. In the Mountain section the incidence was the same as the median but in all other sections the incidence was considerably below the 1943-47 median. For the country as a whole the current incidence was the lowest since 1941 when 225 cases were reported for these same weeks. The current incidence compares very favorably with the average number of cases (approximately 275) for non-epidemic years; the 1943-47 median contains three years of unusually high meningitis incidence.

Scarlet Fever.—This disease continued on its downward trend, the number of cases (8,312) reported for the four weeks ended April 24 being below the record low incidence of 1947 (9,898 cases). In each section of the country the current incidence was considerably below the normal seasonal incidence. This disease has been on a steady decline since 1944 and for this particular period the incident was the lowest in the 20 years for which these data are available.

Smallpox.—Kansas and North Carolina each reported two cases of smallpox and Nebraska, Wyoming, and Arizona one each during the current four weeks. There were 38 cases reported during the corresponding period in 1947 and the median for the preceding five years was 54 cases. During this period in 1947 there was a slight outbreak of smallpox around New York City, the first outbreak in New York State since 1939, and 13 cases were also reported from Texas during these weeks. For the country as a whole the current incidence is the lowest on record for this period.

Typhoid and paratyphoid fever.—The number of cases of these diseases increased from 166 cases during the preceding four weeks to 225 during the current four-week period. The number

of cases was 1.4 times the 1947 incidence for the same weeks and slightly below the median for the preceding five years. The greatest increases over the 1947 figure occurred in the South Atlantic and West South Central sections with minor increases in all other sections except the New England, Mountain, and Pacific sections. Compared with the preceding five-year median, the current incidence was higher than the median in New England, West North Central, South Atlantic, and West South Central sections; in other sections the number of cases were about the same or below the medians.

Whooping cough.—For the four weeks ended April 24 there were 8,001 cases of whooping cough reported, as compared with 10,545 in 1947 and a median of 10,035 for the corresponding weeks in the preceding five years. In the West South Central section the number of cases (2,172) was 1.9 times the seasonal expectancy and a few more cases than might normally be expected occurred in the West North Central and Mountain sections, but in all other sections the incidence was relatively low.

Mortality, All Causes

For the four weeks ended April 24 there were 37,407 deaths from all causes reported to the National Office of Vital Statistics by 93 large cities. The median number for the years 1945-47 was 36,731 deaths. During the first two weeks of the four-week period the number of deaths was considerably above the preceding 3-year median, but during each of the last two weeks the number was below the median. For the entire four week period, increase over the median was about 1.8%.

NEWS AND ANNOUNCEMENTS

Officers of the Rocky Mountain Pediatric Society for 1948 have been elected as follows: Dr. John M. Nelson, President; Dr. Galen C. Garver, Vice-President; and Dr. Edwin T. Williams, Secretary-Treasurer. Monthly meetings are scheduled at the Children's Hospital or the Colorado General Hospital except during July, August and September.

* * *

Dr. Charles Bradley, Director of the Emma Pendleton Bradley Home in East Providence, R.I., for the past 15 years, has joined the staff of the University of Oregon Medical School as Associate Professor of Pediatrics and Psychiatry. His duties are to involve the teaching of child psychiatry in the Medical School program; and, as part of the cooperative effort of the Medical School and the State Board of Health, he will have charge of a new state program in child psychiatry.

Dr. Maurice W. Laufer, who has been Clinical Director at the Bradley Home for the past two years, will suceed Dr. Bradley as Director.

* * *

New York, N.Y.—A reduction in the number of child accidents, both fatal and nonfatal, is the objective of an intensive child safety campaign to be launched this fall by the Metropolitan Life Insurance Company with the cooperation of the U. S. Children's Bureau, the American Academy of Pediatrics, and the National Safety Council. Accidents are the leading cause of death among children of more than 1 year of age, with death rates per 100,000 population far surpassing those of any other cause. For example, in 1946, according to the experience of the Metropolitan among its Industrial policyholders, the accident death rate among children from 1 to 4 was 48.1 per 100,000, as compared with a rate of 28.2 per 100,000 for pneumonia, the next leading cause of death. It is significant that at this age group there has been little improvement in the past 15 years, although the death rate from disease has been cut approximately 67%.

In the age group 5 to 9, the death rate for accidents was 25.7 per 100,000 as compared with a rate of 4.6 for rheumatic fever and organic heart disease, the next cause. In the age group 10 to 14, the death rate for accidents was 20.8, and that for rheumatic fever and organic heart disease, 7.2.

The present relatively low death rates from all nonaccident causes, as compared with those of but a few years ago, are the result of advances in medical science and concentrated efforts in the field of child health. Efforts must now be intensified to bring about a reduction in the number of child accidents as well. The program is planned to encourage public health, medical, safety, and other organizations, as well as the general public, to give even greater attention to the child safety phase of the child health program.

As part of the campaign the Metropolitan has prepared a 12-page illustrated booklet, "Help Your Child to Safety." While the booklet is addressed to parents and stresses the importance of cooperation on the part of all members of the family regarding child safety, it also emphasizes some significant ways of combatting physical hazards and unsafe practices resulting in child injuries. The Metropolitan Field Force throughout the United States will cooperate in this campaign, as it has in so many others, by distributing the booklet and in other appropriate ways will help to make the public aware of what can be done to cut down the tremendous toll of child accidents.

Supplies of the booklet and copies of statistical charts, prepared talks, suggested press releases, and other source material will be available upon request by September 1 for use in local organized child safety programs.

* * *

The following doctors were certified by the American Board of Pediatrics after their examinations in Cleveland, Ohio, on April 23, 24, and 25, 1948. The total number certified is now 2791.

Alfred B. Amler, 62 Greenridge Ave., White Plains, N.Y.
Raymond B. Anderson, Plaza Time Bldg., 411 Alameda, Kansas City, Mo.
Emanuel Berger, 1745 N. Fourth St., Philadelphia, Pa.
Abraham Berkow, 417 W. Main St., Hackensack, N.J.
Benjamin C. Berliner, 163 E. Rockaway Rd., Hewlett Harbor, N.Y.
Joseph Bitman, 7748 Cedarbrook St., Philadelphia, Pa.

Louis C. Burket, 322 Fifth Ave., Altoona, Pa.
Henry Burkhart, 337 Appleton St., Holyoke, Mass.
Nathan Cabot, 1956 McGraw Ave., Bronx, N.Y.
Harold A. Cassady, 2728 Erie Ave., Cincinnati 8, Ohio
Mary Clark, 990 Hardy St., Hattiesburg, Miss.
Elizabeth Conrad, 409 Reynolds Bldg., Winston-Salem 3, N.C.
Douglas S. Damrosch, Babies' Hospital, New York, N.Y.
William D. DeVaux, 3849 Hyde Park Ave., Cincinnati 9, Ohio.
Ernest H. Dreyfuss, 1525 E. 53rd St., Suite 625, Chicago 15, Ill.
Albert M. Edmonds, 399 Westfield Ave., Elizabeth, N.J.
Jackson K. Eto, 634 N. Grand Blvd., St. Louis, Mo.
Abraham Gilner, 1328 49th St., Brooklyn, N.Y.
M. Elizabeth Grant, 12 S. Union St., Cambridge, N.Y.
Helen Hardenbergh, 950 The Alameda, San Jose, Calif.
Charles H. Hollis, 57 Jackson St., Lawrence, Mass.
Edwin L. Kendig, Jr., 5707 York Rd., Richmond, Va.
Eva Landsberg, 925 Westend Ave., New York, N.Y.
Carolyn M. McCue, 1030 W. Franklin St., Richmond, Va.
Ethel M. Madden, 1412 Bull St., Columbia, S.C.
Noah Miller, 193 W. Market St., Akron, Ohio.
William J. Morrow, Dept. of Ped., Univ. Hospital, Ann Arbor, Mich.
Edward J. Muldoon, 230 Chestnut Blvd., Cuyahoga Falls, Ohio
Francis D. Nance, 1133 Punchbowl St., Honolulu, Hawaii
Alice C. Nauen, 41 Concord Ave., Cambridge, Mass.
William W. Owens, 905 Union St., Brooklyn, N.Y.
Nicholas E. Pingitore, 39 Fifth Ave., New York, N.Y.
Marlin H. Poindexter, Jr., Fargo Clinic, 807 Broadway, Fargo, N.D.
Charles Rosenfeld, 5238 Parkside Ave., Philadelphia, Pa.
Hubert A. Royster, Jr., The Mermont Apartments, Bryn Mawr, Pa.
Allan A. Rubenstein, 229-02 Merrick Rd., Laurelton, N.Y.
Isaac H. Schwartz, 32 Court St., New Bedford, Mass.
Benjamin B. Shaver, 141 Club Dr., San Antonio, Tex.
Robert C. Storrs, Hitchcock Clinic, Hanover, N.H.
Sidney Wachtell, 1046 Grand Concourse, Bronx, N.Y.
Thomas H. Weller, Children's Hospital, Boston, Mass.
James A. Wolff, Children's Hospital, Boston, Mass.

BOOK REVIEWS

THE PROBLEM OF CEREBRAL PALSY TODAY, M. A. Perlstein, M.D., with assistance of William McPeak, 57 pages, illustrations. The National Society for Crippled Children and Adults, Chicago 3, 1947.

Dr. Perlstein presents the problem in the care of cerebral palsy patients as it confronts us today. The monograph is concise, well written, and reveals the author's comprehensive knowledge of the subject.

Part one is concerned with a general description of the problem and discusses the causes, types, prognosis, incidence and other pertinent information and observations. Our present facilities for care are outlined, and this picture is a sorry one indeed. Only about 10% of these unfortunate individuals receive adequate care at the present time.

Part two offers a well thought out and sensible plan to provide effective care. The proposed In-Patient Hospital-Schools and Out-Patient Clinic-Schools administered at state levels seem to offer a method of care far superior to any plan existing in most of our states today. There are a few states which have already inaugurated this or a similar plan.

The final three parts discuss Professional Training for Cerebral Palsy, Research Needs, and finally, Cerebral Palsy as a Socio-Economic Problem. The booklet is well worth the attention of all lay and professional people who are interested in the health and welfare of children.

G. F. MUNNS

DIAGNOSTIK DER KINDERKRANKHEITEN MIT BESONDERER BERÜCKSICHTIGUNG DES SÄUGLINGS, Dr. E. Feer, 5th Edition, $8.00, 427 pages, 285 illustrations (4 in color), Springer-Verlag, Wien. 1, 1947.

In the fifth edition of "Diagnostik der Kinderkrankheiten" Dr. Feer has once again attempted to present the elements of pediatric diagnosis in the form of a timely practical handbook for medical students and busy practitioners. Following the semeiotic arrangement employed in previous editions the author draws on his extensive pediatric experience to provide a wealth of accurate diagnostic detail in a refreshingly familiar style. Although the spectrum of pediatric diagnosis is, in general, covered admirably, certain important aspects are neglected. Problems peculiar to the diagnosis of virus and parasitic infections in childhood receive little attention; only the bare elements in the diagnosis of deficiency diseases and endocrine disturbances are discussed; and the fields of acute and chronic poisoning, as well as the subject of malignancy in childhood, are incompletely elucidated. In striking contrast to most modern pediatric works the homely technics of diagnosis are emphasized with little space being given to laboratory diagnostic aids. The accompanying photographs including several color photos are technically adequate and illustratively impressive.

In spite of its few deficiencies Dr. Feer's text will continue to fulfill a real need in the armamentarium of the German clinician.

R. A. GOOD

THE DISPENSATORY OF THE UNITED STATES OF AMERICA, Arthur Osol, Ph.G., M.S., Ph.D., and George E. Farrar, Jr., M.D., 24th edition. $16.50, J. B. Lippincott Company, Philadelphia 5, Pa., 1947.

This edition is based on the U.S.P. XIII, N.F. VIII, N.N.R., 1947, and the British Pharmacopoeia, 1932, and its addenda. The significant change in editorial policy is the enlargement of that portion of each monograph devoted to a discussion of therapeutic uses and dosage of drugs, and an increased emphasis placed upon precautions to be observed during drug administration. Another new feature is the inclusion of the name of the manufacturer or distributor whose trade name or trade mark of the drug being discussed. It contains complete medical and pharmaceutical information of every drug used in medicine.

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